Available online at www.sciencedirect.com

SCIENCE DIRECT®

Carbohydrate Research 340 (2005) 2670–2674

Carbohydrate
RESEARCH

Note

Mild one-pot preparation of glycosyl bromides

Mo Hunsen,* David A. Long, Christopher R. D'Ardenne and Amanda L. Smith

Department of Chemistry, Kenyon College, Gambier, OH 43022, USA

Received 25 May 2005; accepted 15 September 2005
Available online 10 October 2005

Abstract—Mild one-pot protocols for the preparation of glycosyl bromides and alkyl bromides via in situ generation of HBr is reported here.

Keywords: Acetyl bromide; Acetobromination; Glycosyl bromides; Carbohydrate; One pot; In situ; HBr

Glycosyl bromides are important intermediates in carbohydrate chemistry. For example, α-glycosyl bromides are used as starting materials in the synthesis of glycosides and oligosaccharides, β-glycosyl halides, glycals, and 2-acetoxyglycals (Scheme 1). Oligosaccharides are increasingly becoming important in the pharmaceutical industry, and the glycals, acetoxyglycals, and α- and β-glycosyl halides are key intermediates in the synthesis of oligosaccharides and glycoconjugates.

Current methods for the preparation of glycosyl bromides include treatment of the free saccharides with AcBr,[1,2] AcBr–AcOH,[3,4] or Ac_2O–HBr–AcOH,[5,6] or treatment of the peracetylated saccharides with HBr–AcOH[7] or $BiBr_3$–Me_3SiBr.[8] The above methods involve the use of a heavy metal and/or transportation, generation, and/or use of excess HBr, which is a corrosive gas, and our experience with the above conditions is not a pleasant one due to the toxic fumes. In light of the versatility and widespread use of glycosyl bromides as key intermediates, a milder protocol for their preparation is still needed.

We report here mild and efficient one-pot protocols for the preparation of glycosyl bromides from the free sugars or their peracetates via in situ generation of HBr from an alcohol and acetyl bromide. We also show that alkyl bromides can be cleanly prepared from alkenes using the same protocol.

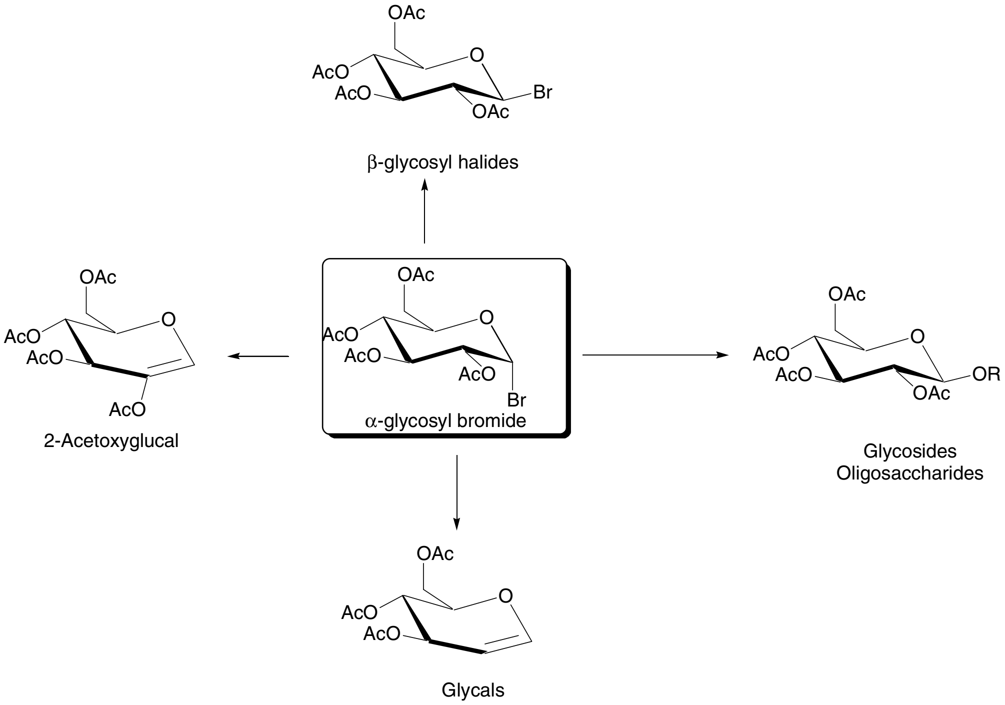
In the first protocol (Table 1, Scheme 2), free sugars were directly and effortlessly converted to the corresponding α-glycosyl bromides. First, acetic anhydride (1.2 equiv per OH group) and a catalytic amount of $HClO_4$ were added to the free sugars in acetic acid, and the reaction mixture was stirred for 30 min. Acetyl bromide (3 equiv) and methanol (3.4 equiv) were then added, and after 90 min the solvent was removed by a rotary evaporator to deliver the glycosyl bromides that were pure enough for further use. As shown in Table 1, glycosyl bromides of monosaccharides (entries 1 and 2), β-linked disaccharides (entries 3 and 4), and α-linked di- and trisaccharides (entries 5 and 6) were prepared in near-quantitative yields. It is worth mentioning that our attempt to use the hydroxyl groups of the free sugar itself to generate HBr from acetyl bromide resulted in the partial hydrolysis of the glycosidic bonds of di- and trisaccharides. The use of methanol with acetyl bromide solved this problem. Anhydrous ethanol worked equally well. Protocol 2 (Table 1, Scheme 3) is another alternative to protocol 1, and it involves the addition of AcBr and methanol to acetic acid to generate HBr, followed by addition of the free sugars and Ac_2O (1.2 equiv per OH group) to deliver the glycosyl bromides. Protocol 1 was found to be better than protocol 2 for galactose and maltotriose.

In the third protocol (Table 2, Scheme 4), peracetates of mono- and disaccharides were cleanly converted to the corresponding α-glycosyl bromides using a mixture of acetyl bromide and methanol in acetic acid. The

---

* Corresponding author. Tel.: +1 7404275091; fax: +1 7404275731; e-mail: hunsenm@kenyon.edu

0008-6215/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2005.09.016



Scheme 1.

products obtained after evaporation of the solvent were pure enough for further applications. It is noteworthy that no hydrolysis of glycosidic bonds was observed under these conditions. For galactose, the best protocol was found to be protocol 3, as protocols 1 and 2 delivered a mixture of the pentaacetate and the galactosyl bromide with a rather lower yield that improved slightly (73%) when the reaction was carried out in an ice bath.

As an extension of this study, we have used the in situ generated HBr to cleanly convert an alkene to alkyl bromide (see protocol 4, Scheme 5). In this case, AcBr (1.05 equiv) and CH_3OH (1.05 equiv) were added to dichloromethane to generate HBr in situ, followed by the addition of cyclohexene. Bromocyclohexane was quantitatively obtained after the workup. Further investigation on hydrobromination reactions is in progress and will be reported in due course.

In summary, we have reported facile and clean one-pot protocols for the preparation of glycosyl bromides using the free sugars and the peracetylated sugars as starting materials. We have also shown that a modified protocol cleanly converts an alkene to an alkyl bromide.

1. Experimental

1.1. Representative experimental protocol 1

To anhydrous D-glucose (2.0 g, 11.10 mmol) in AcOH (20 mL) were added Ac_2O (6.5 mL, 68.76 mmol) and $HClO_4$ (four drops), and the reaction mixture was stirred at rt for 30 min. AcBr (2.5 mL, 33.15 mmol) and CH_3OH (1.6 mL, 39.90 mmol) were then added, and the reaction mixture was stirred at rt (protected from light) for 90 min (followed by TLC in hexane–EtOAc). The solvent was then evaporated to give 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4.6 g, 100% yield: 98% desired product 2% peracetate based on NMR spectra).

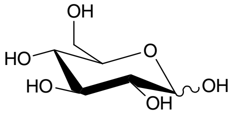
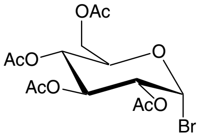
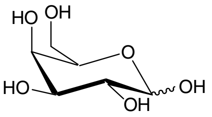
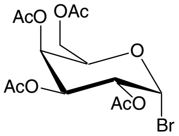
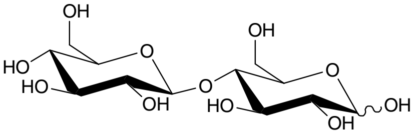
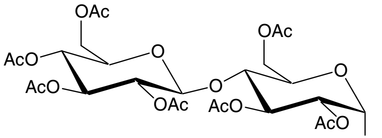
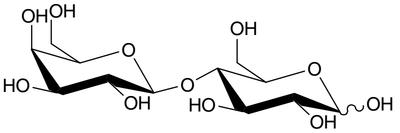
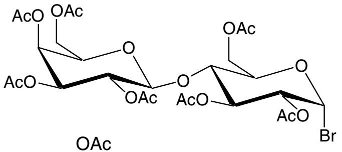
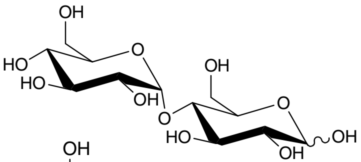
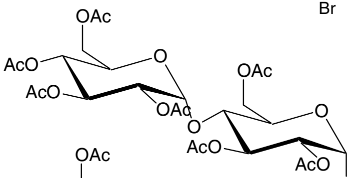
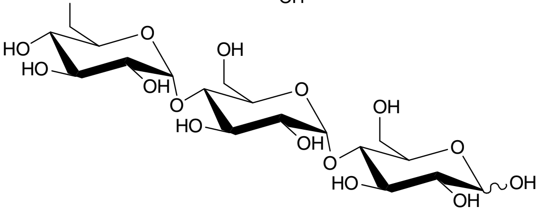
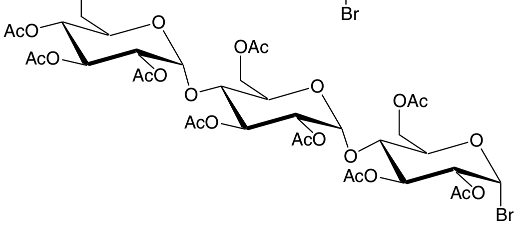
1.2. Representative experimental protocol 2

Acetyl bromide (0.92 mL, 12.3 mmol) and CH_3OH (0.5 mL, 12.30 mmol) were added to AcOH (10 mL) and stirred at rt (protected from light) for 15 min, followed by addition of D-maltose (1.0 g, 3.08 mmol) and Ac_2O (3.4 mL, 35.97 mmol). The reaction mixture was further stirred for 90 min at rt (followed by TLC in hexane–EtOAc), and the solvent was evaporated to give 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-D-maltosyl bromide (2.15 g, 100% yield: 95% desired product and 5% peracetate based on NMR spectra).

1.3. Representative experimental protocol 3

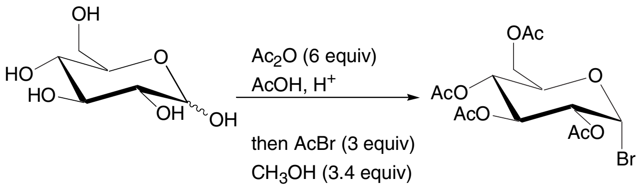
To D-cellobiose octaacetate (3.9 g, 5.58 mmol) dissolved in AcOH (20 mL) were added AcBr (1.3 mL, 17.52 mmol) and CH_3OH (0.3 mL, 7.01 mmol), and the reaction mixture was stirred at rt (protected from light) for 2 h (followed by TLC in hexane–EtOAc).

Table 1. One-pot acetobromination of free sugars

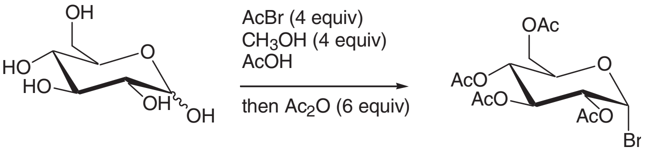
Entry	Reactant	Product	% Yield[a] protocol		
			1	2	Ref.[b]
1			98	97	8
2			65	34	8
3			90	—	10
4			93	95	5
5			92	95	8
6			95	88	9

[a] The percent yields are for the glycosyl bromides based on ^{1}H NMR spectroscopy and the remaining material was their peracetate.

[b] All the products are known compounds and their physical properties and NMR spectra are consistent with literature.



Scheme 2.



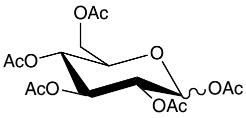
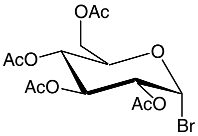
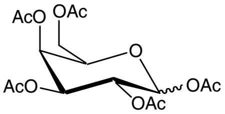
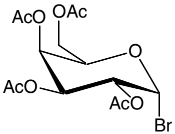
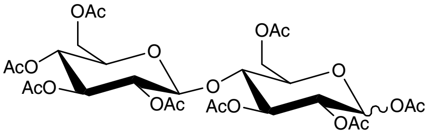
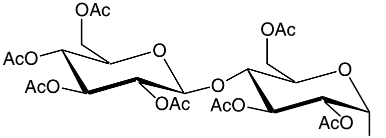
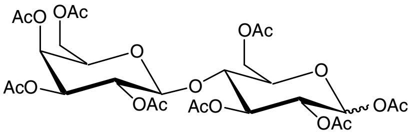
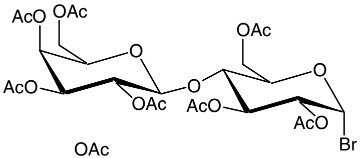
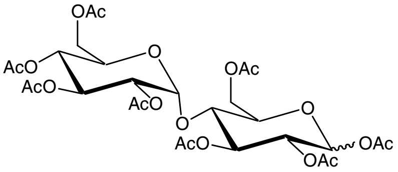
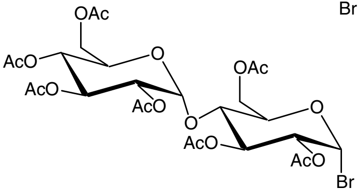
Scheme 3.

The solvent was then evaporated to give 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-D-cellobiosyl bromide (4.1 g, 100% yield: 95% desired product and 5% peracetate based on NMR spectra).

1.4. Representative experimental protocol 4

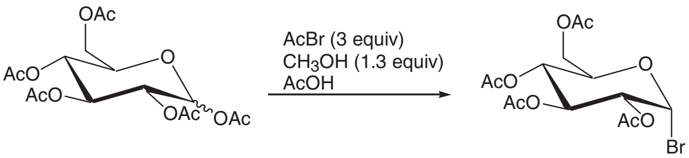
Acetyl bromide (0.79 mL, 1.05 mmol) and MeOH (0.43 mL, 10.5 mmol) were added to CH_2Cl_2 (30 mL) and stirred at rt for 10 min (protected from light). Cyclohexene (1.01 mL, 10 mmol) was then added, and the reaction mixture was stirred overnight at rt, washed with 5% aq sodium bicarbonate and brine, respectively, and concentrated to give 1.56 g of bromocyclohexane (96% yield). The ^{1}H and ^{13}C NMR spectra of the product show that it is a very clean product and is consistent with the spectra in Aldrich.[11]

Table 2. One-step acetobromination of peracetates of sugars

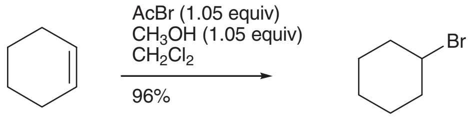
Entry	Reactant	Product	% Yield[a]	Ref.[b]
1			98	8
2			85	8
3			94	10
4			85	5
5			100	8

[a] The percent yields are for the glycosyl bromides based on ^{1}H NMR spectroscopy and the remaining material was their peracetate.

[b] All the products are known compounds and their physical properties and NMR spectra are consistent with literature.



Scheme 4.



Scheme 5.

Acknowledgments

M.H. thanks Kenyon College for the generous start-up fund. D.L. and A.S. thank Kenyon College for Summer Science Fellowships.

References

1. Ditmar, R. *Monatsh. Chem.* **1902**, *23*, 865–876.
2. Fischer, E.; Fischer, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2521–2536.
3. Koto, S.; Morishima, N.; Irisawa, T.; Hashimoto, Y.; Yamazaki, M.; Zen, S. *Nippon Kakgaku Kaishi* **1982**, 1651–1656.
4. Koto, S.; Morishima, N.; Shichi, S.; Haigoh, H.; Hirooka, M.; Okamoto, M.; Higuchi, T.; Shimizu, K.; Hashimoto, Y.; Iriawa, T.; Kawasaki, H.; Takahashi, Y.; Yamazaki, M.; Mori, Y.; Kudo, K.; Ikegaki, T.; Suzuki, S.; Zen, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3257–3274.
5. Kartha, C. P. R.; Jennings, H. J. *J. Carbohydr. Chem.* **1990**, *9*, 777–781.
6. Larsen, K.; Olsen, C. E.; Motawia, M. S. *Carbohydr. Res.* **2003**, *338*, 199–202.
7. Fischer, E. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 1898–1904.
8. Montero, J. L.; Winum, J. Y.; Leydet, A.; Kamal, M.; Pavia, A. A.; Roque, J. P. *Carbohydr. Res.* **1997**, *297*, 175–180.
9. Farkas, E.; Janossy, L.; Harangi, J.; Kandra, L.; Liptak, A. *Carbohydr. Res.* **1997**, *303*, 407–415.

10. (a) Scheurer, P. G.; Smith, F. *J. Am. Chem. Soc.* **1954**, *76*, 3224; (b) Malet, C.; Viladot, J. L.; Ochoa, A.; Gallego, B.; Brosa, C.; Planas, A. *Carbohydr. Res.* **1995**, *274*, 285–301.
11. *Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra*; Pouchert, C., Behnke, J., Eds.; Aldrich Chemical: Milwaukee, 1993; Vol. 1, p 152.