Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 3931–3934

TETRAHEDRON LETTERS

Ferric chloride: a mild and versatile reagent for the formation of 1,6-anhydro glucopyranoses

Pedro O. Miranda, Ignacio Brouard, Juan I. Padrón* and Jaime Bermejo*

Instituto Universitario de Bio-Orgánica 'Antonio González', Instituto de Productos Naturales y Agrobiología del C.S.I.C., Avenida Astrofísico Fco Sánchez 3, 38206 La Laguna, Tenerife, Canary Islands, Spain

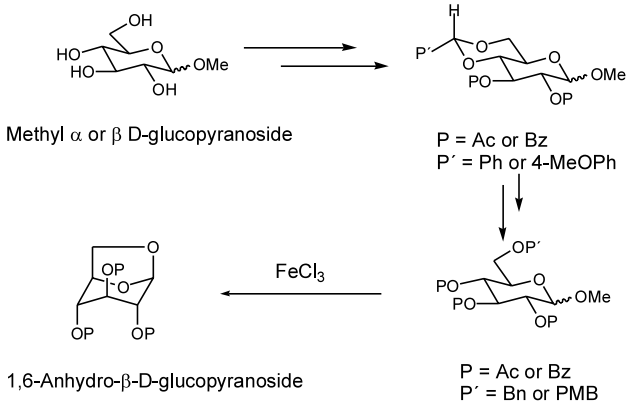
Received 30 December 2002; accepted 7 March 2003

Dedicated to the memory of Professor Antonio G. González

Abstract—A novel method for the preparation of 1,6-anhydro glucopyranoses (mono- and disaccharides) utilizing anhydrous $FeCl_3$ as Lewis acid is described. Treatment of methyl 6-*O*-benzyl and 6-*O*-*p*-methoxybenzyl-α/β D-glucopyranosides derivatives with $FeCl_3$ in CH_2Cl_2 at room temperature and 40°C afforded 1,6-anhydro glucopyranosides in moderate to good yields, through a debenzylation and intramolecular glycosidation in one step. A plausible reaction pathway is proposed. © 2003 Published by Elsevier Science Ltd.

1,6-Anhydropyranoses have proven to be valuable synthons for the preparation of biologically important and structurally diverse natural products (e.g. rifamycin S, indanomycin, zaragozic acid, etc.)[1] as well as for modified sugars.

1,6-Anhydro-β-D-glucopyranose (levoglucosan) was prepared first by Tanret[2] as a product of the alkaline decomposition of several naturally occurring glucosides. It was obtained later from starch and cellulose by pyrolitic vacuum distillations.[3] It can be also obtained by alkaline treatment of phenyl β-D-glucopyranoside,[4] of 6-*O*-tosyl glucose,[5] or of many other glucose derivatives. In a general way, 1,6-anhydropyranoses can be obtained under basic conditions,[6] acid conditions[7] and through intramolecular anomeric *O*-alkylation.[8]



Scheme 1. Strategy for the preparation of 1,6-anhydro-β-D-glucopyranoside.

1,6-Anhydroglucopyranoses are usually prepared by installing a leaving group at 6-*O* or 1-*O* and its further displacement in an intramolecular reaction (intramolecular glycosidation or otherwise). The reaction of 6-*O*-leaving group glucopyranoses is not a true intramolecular glycosylation because the glycosidic bond is not formed; instead, the 1-*O*/6-C bond is formed by intramolecular nucleophilic substitution (intramolecular anomeric *O*-alkylation).

Different leaving groups can be used such as tosyl, trityl, acetyl, etc. at the 6-*O*-position and phenyl, acetyl, and methyl at the 1-*O*-position. In all cases it is necessary to introduce the leaving group except with the *O*-methyl group, which is incorporated in the starting material. Several precedents are reported in the literature using the *O*-methyl group in the α or β anomeric configuration as leaving group.[7b,9]

We present herein a method to obtain 1,6-anhydro glucopyranosides using methyl 6-*O*-benzyl and 6-*O*-*p*-methoxybenzyl-α/β D-glucopyranosides derivatives hav-

* Corresponding authors. Tel.: (34) 922 250766; fax: (34) 922 318571; e-mail: jbermejo@ull.es

0040-4039/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4039(03)00821-9

ing the methoxyl as a leaving group and anhydrous $FeCl_3$ as Lewis acid through a debenzylation and intramolecular glycosidation in one step.[10] This method is effective in mono- and disaccharides, for which fewer precedents exist.[11]

The monosaccharide models were prepared from α and β-D-glucopyranosides through formation of benzylidene acetal,[12] acylation (benzoylation or acetylation), regioselective reductive ring opening of benzylidene and final acylation (Scheme 1).

A modified Koenigs–Knorr method[13] was chosen for the syntheses of disaccharide models. Such disaccharides were synthesized from the 2,3,4,6-tetrakis-*O*-(*p*-bromobenzoyl)-α-D-glucopyranosyl bromide[14] with the corresponding methyl β-D-glucopyranoside derivatives in the presence of silver trifluoromethanesulfonate.

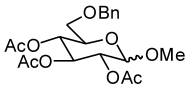
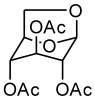
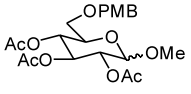
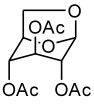
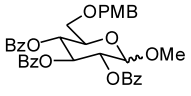
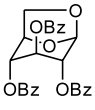
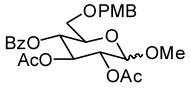
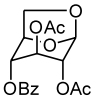
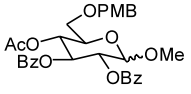
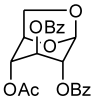
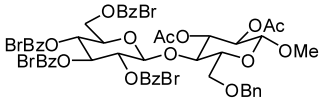
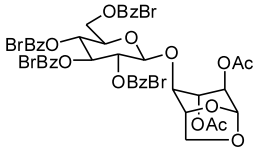
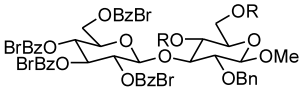
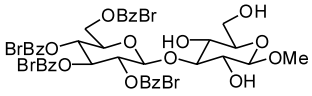
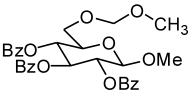
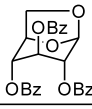
The results of this intramolecular glycosidation in various substrates under our conditions are summarized in Table 1.

We obtained levoglucosan triacetate (2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranoside) from methyl 2,3,4-tri-*O*-acetyl-6-*O*-benzyl α/β D-glucopyranoside in higher yield from β methyl than from α according to the higher reactivity of β anomer[15] (Table 1, entry 1). The same behaviour was observed using the *p*-methoxybenzyl group (Table 1, entries 2–5). The ^1H and ^{13}C NMR spectra of our levoglucosan triacetate matched with those obtained from the acetylation of commercially available levoglucosan.

Due to a precedent to form 1,6-anhydrofuranoses from methyl 2,3,5-tri-*O*-benzoyl-6-*O*-benzyl β-D-galactofuranoside using $SnCl_4$ as Lewis acid,[16] and the fact that this Lewis acid gave the best yields described in the literature, we decided to use it for a comparison with anhydrous ferric chloride. In all cases the $SnCl_4$ produced 1,6-anhydropyranoses in lower yields (ca. 30%) than anhydrous $FeCl_3$.

It is noteworthy to mention that the role of the benzyl or *p*-methoxybenzyl group is essential to achieving the reported transformation, since when the 6-*O* position is

Table 1. Synthesis of 1,6-anhydroglucopyranoses (mono- and disaccharides)

entry	Substrate	Conditions[a]	Product	Yield[b] %
1		40 °C, t_β= 20, t_α= 180		63 (from β-OMe) 32 (from α-OMe)
2		40 °C, t_β= 15, t_α= 120		65 (from β-OMe) 40 (from α-OMe)
3		40 °C, t_β= 15 , t_α= 120		54 (from β-OMe) 50 (from α-OMe)
4		40 °C, t_β= 10, t_α= 120		68 (from β-OMe) 30 (from α-OMe)
5		40 °C, t_β= 10, t_α= 120		60 (from β-OMe) 50 (from α-OMe)
6		rt, t = 10		70
7	 R = H R = benzylidene group (CHC_6H_5)	rt, t = 20		70 (from R = H) 85 (from R=CHC_6H_5)
8		rt, t = 10		54

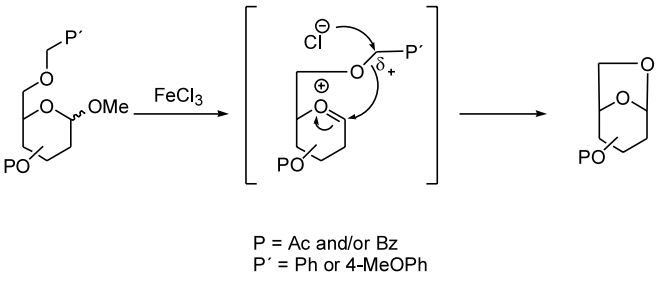
[a] time (t) in minutes. [b] Isolated yields

unprotected or is a benzylidene group the reaction did not occur (entry 7) and the corresponding triol was obtained. Precedents exist where these groups are able to stabilize a positive charge at the benzylic position.[17] With these results in mind we decided to use other stabilizing positive charge groups, such as methoxymethyl (MOM),[18] to verify this fact. With the MOM group (entry 8) the 1,6-anhydro was produced in 54% yield supporting the possible formation of a positive charge at the position commented above. A nucleophilic attack of a chlorine at benzylic position following by an intramolecular glycosidation trapping the oxocarbenium intermediate is the basis of our tentative explanation (Scheme 2).[19]

In all the monosaccharide models better yields were obtained using methyl β instead of methyl-α-D-glucopyranoside, (Table 1, entries 1–5). The best yield was obtained in the disaccharide model (entry 6) to give 2,3-di-*O*-acetyl-2′,3′,4′,6′-tetrakis-*O*-(*p*-bromobenzoyl)-1,6-anhydro-β-cellobiose.

Except in the disaccharide model, the reaction to form 1,6-anhydropyranoses was slower at room temperature than at 40°C. A control of the reaction temperature permitted us to differentiate the debenzylation process against the intramolecular glycosidation and anomerization. In the disaccharide case (entry 6), when the reaction was run at room temperature 1,6-anhydro disaccharide was obtained in good yields, while at 0°C the debenzylated disaccharide methyl β-D-glucopyranosyl (1–4) 2,3,4,6-tetrakis-*O*-(*p*-bromobenzoyl)-β-D-glucopyranoside, was obtained in excellent yield (95%).[20]

In conclusion, we have developed an efficient reaction to obtain 1,6-anhydro glucopyranosides (mono- and disaccharides). Following the strategy of Scheme 1 and applying this method we can access 1,6-anhydro-β-D-glucopyranosides derivatives (Table 1, entries 1–5) or the most unusual 1,6-anhydrodisaccharide where the cleavage of acetates can be accomplished in the presence of other esters such as benzoates to obtain synthons useful in organic synthesis, such as we carried out with the 1,6-anhydro disaccharide of entry 6.[21]



Scheme 2.

Acknowledgements

This work was supported in part by FEDER Grant No. 1FD 1997-1831 (J.B.B.). I.B. gratefully acknowledges the Dirección General de Universidades e Investigación del Gobierno de Canarias (Spain) for a fellowship. We are indebted to Dr. Jesús Trujillo Vázquez for his generous help with the disaccharide models.

References

1. (a) Caron, S.; Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9126–9134; (b) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960–5968; (c) Shang-Cheng, H.; Shankar, R. T.; Fa-Chen, C.; Shu-Wen, C.; Jinq-Chyi, L.; Cheng-Chung, W.; Yuh-Sheng, W. *J. Am. Chem. Soc.* **2001**, *123*, 3153–3154; (d) Kroutil, J.; Trnka, T.; Budesinsky, M.; Cerny, M. *Eur. J. Org. Chem.* **2002**, 2449–2459.
2. Tanret, C. *Compt. Rend.* **1894**, *119*, 158.
3. Pictet, A.; Sarasin, J. *Helv. Chim. Acta* **1918**, *1*, 78.
4. (a) Coleman, G. H.; McCloskey, C. M.; Kirby, R. *Ind. Eng. Chem.* **1944**, *36*, 1040; (b) Coleman, G. H. In *Methods in Carbohydrate Chemistry II*; Whistler, R. L.; Wolfrom, M. L.; BeMiller, J. N., Eds.; Academic Press: New York, London, 1963; p. 397.
5. Akagi, M.; Tejima, S.; Haga, M. *Chem. Pharm. Bull.* **1962**, *10*, 905–906.
6. (a) Fujimaki, I.; Ichikawa, Y.; Kuzuhara, H. *Carbohydr. Res.* **1982**, *101*, 148–151; (b) Funabashi, M.; Nagashima, H. *Chem. Lett.* **1987**, 2065–2068; (c) Zottola, M. A.; Alonso, R.; Vite, G. D.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 6123–6125; (d) Álvarez, E.; Pérez, R.; Rico, M.; Rodríguez, R. M.; Suárez, M. C.; Martín, J. D. *Synlett* **1996**, 1082–1084; (e) Li, C.; Yu, B.; Zhang, G. T.; Hui, Y. Z. *Chinese J. Chem.* **1998**, 381–384.
7. (a) Rao, M. V.; Nagarajan, M. *Carbohydr. Res.* **1987**, 141–144; (b) Horita, K.; Sakurai, Y.; Nagasawa, M.; Hachiya, S.; Yonemitsu, O. *Synlett* **1994**, 43–45; (c) Léger, S.; Omeara, J.; Wang, Z. *Synlett* **1994**, 829–830; (d) Caron, S.; McDonald, A. I.; Heathcock, C. H. *J. Org. Chem.* **1995**, *60*, 2780–2785.
8. Jung, K. H.; Müller, M.; Schmidt, R. R. *Chem. Rev.* **2000**, *100*, 4423–4442 and references cited therein.
9. (a) Schmidt, R. R.; Michel, J.; Rücker, E. *Liebigs Ann. Chem.* **1989**, 423–428; (b) Sarkar, S. K.; Choudhury, A. K.; Mukhopadhay, B.; Roy, N. *J. Carbohydr. Chem.* **1999**, *18*, 1121–1130.
10. **General procedure**. To a stirred solution of the substrate in dry CH_2Cl_2 (0.03 M) 2 equiv. of anhydrous $FeCl_3$ were added under dry Ar and the reaction temperature was selected. The reaction was quenched by addition of water and stirred for a couple of minutes and then extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems).
11. Fujimaki, I.; Yoshitaka, I.; Kuzuhara, H. *Carbohydr. Res.* **1982**, *101*, 148–151.

12. Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371–2374.
13. (a) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *53*, C13–C16; (b) Garegg, P. J.; Norberg, T. *Acta Chem. Scand.* **1979**, *B33*, 116–118; (c) Padrón, J. I.; Morales, E. Q.; Vazquez, J. T. *J. Org. Chem.* **1998**, *63*, 8247–8258.
14. Morales, E. Q.; Padrón, J. I.; Trujillo, M.; Váquez, J. T. *J. Org. Chem.* **1995**, *60*, 2537–2548.
15. (a) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press, Inc: Boca Raton, 1995; (b) McPhail, D. R.; Lee, J. R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1992**, *114*, 1905–1906.
16. Sarkar, S. K.; Choudhury, A. K.; Mukhopadhayay, B.; Roy, N. *J. Carbohydr. Chem.* **1999**, *18*, 1121–1130.
17. Lergenmüller, M.; Nukada, T.; Kuramochi, K.; Dan, A.; Ogawa, T.; Ito, Y. *Eur. J. Org. Chem.* **1999**, 1367–1376 and references cited therein.
18. Diaz, D.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 743–746.
19. The reaction was monitored by NMR spectroscopy. Using CD_2Cl_2, the ^1H NMR spectra of the reaction mixture revealed resonances corresponding to the 1,6-anhydroglucopyranoside.
20. Padrón, J. I.; Vázquez, J. T. *Tetrahedron: Asymmetry* **1995**, *6*, 857–858.
21. González, A. G.; Brouard, I.; León, F.; Padrón, J. I.; Bermejo, J. *Tetrahedron Lett.* **2001**, *42*, 3187–3188.