



Tin(IV) Chloride Mediated Glycosylation in Arabinofuranose, Galactofuranose and Rhamnopyranose.

Ashish K. Pathak, Yahya A. El-Kattan, Namita Bansal, Joseph A. Maddry* and Robert C. Reynolds*

Organic Chemistry Department, Southern Research Institute, P.O. Box 55305, Birmingham, AL 35255-5305, USA.

Received 24 November 1997; revised 22 December 1997; accepted 23 December 1997

Abstract : Using tin(IV) chloride, *O*-glycosylation reactions were performed on peracylated D-arabinofuranose, D-galactofuranose and L-rhamnofuranose as well as 1-bromo-D-arabinofuranoses at room temperature in good anomeric purities and yields. In these circumstances, this coupling method has certain advantages over standard glycosylation reactions, such as the Koenigs-Knorr methods which use the 1-halosugar (synthesized from the 1-acyl derivative) and toxic mercury salts as the coupling agent.

© 1998 Elsevier Science Ltd. All rights reserved.

The worldwide resurgence of mycobacterial diseases, particularly tuberculosis and drug resistant forms,^{1,2} has led to an interest in characterization of biochemical pathways in these bacteria with the goal of identifying novel targets for the development of new and selective agents.³ The identification of the mycobacterial cell wall polysaccharides and the monosaccharides contained therein (particularly arabinofuranose, galactofuranose, and rhamnopyranose)⁴ has focused interest on the putative glycosyltransferases required for biosynthesis.⁵ These particular sugars are not found in mammalian cells and the associated biosynthetic pathways could be a target for the development of novel inhibitors of mycobacterial cell wall elaboration. Thus, we were interested in the facile synthesis of a number of arabinofuranose-, galactofuranose-, and rhamnopyranose-containing mono- and disaccharides with specific stereochemistry at the anomeric center.

It is well known that Lewis acids activate the anomeric center in peracylated furanose and pyranose sugars leading to the formation of a glycosidic linkage having the 1,2-*trans* configuration.⁶ Tin(IV) chloride, in particular, gives excellent anomeric resolution in many types of sugars during glycosylation.⁷ The high selectivity in the glycosylation reactions using SnCl₄ is attributed to the neighboring group effect of the C-2 substituent *via* formation of an acyloxonium ion with concomitant stabilization of the positive charge on C-1. This also results in effective blockage of one face and leads to 1,2-*trans* glycosylation. However, utilization of SnCl₄ under conditions reported for L-arabinofuranose gave an anomeric mixture of glycosides and were found unsuitable for our purposes.⁸ We next tried conditions reported for nucleoside formation that involved precomplexation of

Table 1 : SnCl₄ Mediated Glycosylation of Some Protected D-Arabinofuranose, D-Galactofuranose and L-Rhamnopyranose Derivatives.

Entry No.	Donor	Acceptor	Time	Yield* (%)	Product
1.		CH ₃ (CH ₂) ₇ OH	1 hr.	63	
2.		ClCH ₂ CH ₂ OH	30 mins.	85	
3.			30 mins.	75	
4.			30 mins.	62	
5.		CH ₃ (CH ₂) ₇ OH	1 hr.	72	
6.			2 hrs.	39	
7.			2 hrs.	43	
8.		CH ₃ (CH ₂) ₇ OH	1 hr.	83	

*Isolated yields.

donor with SnCl_4 followed by slow addition of acceptor and obtained the desired high anomeric purity.⁹ We have thus found that glycosylation reactions with 1-acyl- arabinofuranose, galactofuranose and rhamnopyranose analogs using tin(IV) chloride as the Lewis acid with initial precomplexation gave products of high anomeric purity having 1,2-*trans* configurations in modest to good yields at room temperature. This precomplexation procedure using SnCl_4 has additional advantages over standard glycosylation reactions such as Koenigs-Knorr method that use the 1-halosugar (synthesized in an additional step from the 1-acyl derivative) and toxic mercury salts as the coupling agent.

Herein we report the glycosylation of several protected arabinofuranose, galactofuranose and rhamnopyranose monosaccharides as well as formation of disaccharide analogs. In general, the donor was dissolved in dry acetonitrile and SnCl_4 was added dropwise in an equimolar ratio under argon. The mixture was stirred at room temperature for 15 minutes to complete complexation. An equimolar amount of acceptor in acetonitrile was then added dropwise with stirring after donor precomplexation. Workup involved dropwise addition of a saturated aqueous NaHCO_3 solution while cooling in an ice-bath to precipitate tin salts, followed by filtration through celite. The celite pad was washed with hot chloroform and the combined filtrates washed with water, brine, dried over Na_2SO_4 and evaporated. Flash chromatography of the crude product on silica gel gave the pure glycoside. The anomeric configuration of the resulting glycosides as established by comparison of $J_{1,2}$ coupling constants¹⁰ with analogous compounds from the literature.¹¹ The results are summarized in Table 1.

In *entry 1-3*, 2,3,5-tribenzoyl- α -D-arabinofuranosyl bromide underwent glycosylation with *n*-octanol, 1-chloroethanol and *N*-hydroxyethylphthalimide to give exclusively the expected α -anomeric glycosides in good yields. The coupling of α -D-arabinofuranosyl tetraacetate (*entry 4*) with chloroethyl-2,3-diacetyl- α -D-arabinofuranoside also gave the desired α -disaccharide. Thus, protected α -D-arabinofuranose sugars containing either a bromo or acetyl at the anomeric center are excellent substrates for SnCl_4 mediated glycosylations. The coupling of β -D-galactofuranosyl pentaacetate (*entry 5-7*) with *n*-octanol, 2,3,5-tri-*O*-benzoyl- β -D-octyl-galactofuranoside and 2,3,6-tri-*O*-benzoyl- β -D-octyl-galactofuranoside as acceptors was performed in the presence of SnCl_4 and gave the corresponding β -glycosylated products. When an α,β anomeric mixture of L-rhamnopyranosyl pentaacetate (*entry 8*) was coupled with *n*-octanol, only 2,3,4-triacetyl- α -L-*O*-octyl-rhamnopyranoside was obtained in very good yield. However, when SnCl_4 was used as Lewis acid in the coupling of β -D-galactofuranosyl pentaacetate and 2,3-isopropylidene- α -L-*O*-octyl-rhamnopyranoside, no glycosylation product was observed under several different conditions. Other protecting groups were also utilized to

no avail, and this failure might be attributable to the less reactive hydroxyl group in the 4-position of rhamnose derivatives.

Acknowledgements :

We are thankful to NIH/NIID for the financial support via grant No. 1U19AI4097202 and 1R01AI3866701A1.

References and Notes :

1. World Health Organization, in *Anti-tuberculosis drug resistance in the world*. The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance, 1997.
2. In *Tuberculosis, Pathogens, Protection, and Control*; Bloom, B. R., Ed.; ASM Press : Washington DC, 1994.
3. Young, D. B. *ibid.* 1994; pp. 559-567.
4. Besra, G. S.; Chatterjee, D.; *ibid.* 1994; pp. 285-306.
5. Maddry, J. A.; Suling, W. J.; Reynolds, R. C. *Res. Microbiol.* **1996**, *147*, 106.
6. (a) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *59*, 261. (b) Lederkremer, R. M.; Marino, C.; Varela, O. *Carbohydr. Res.* **1990**, *200*, 227. (c) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Merritt, J. R.; Rao, S.; Roberts, C.; Madsen, R. *Syn Lett* **1992**, 927. (d) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (e) Hanessian, S. Ed. in *Preparative Carbohydrate Chemistry*, Marcel Dekker : New York, 1977.
7. (a) Mortier, C.; Varela, O.; Lederkremer, R. M. *Carbohydr. Res.* **1989**, *189*, 79. (b) Gallo-Rodriguez, C.; Varela, O.; Lederkremer, R. M. *J. Org. Chem.* **1996**, *61*, 1886. (c) Hanessian, S.; Banoub, J. *Tetrahedron Lett.* **1976**, 657. (d) Hanessian, S.; Banoub, J. *Tetrahedron Lett.* **1976**, 661. (e) Honma, K.; Nakazima, K.; Uematsu, T.; Hamado, A. *Chem. Pharm. Bull.* **1976**, *24*, 394.
8. Mizutani, K.; Kasai, R.; Nakamura, M.; Tanaka, O.; Matura, H. *Carbohydr. Res.* **1989**, *185*, 27.
9. Wilson, L. J.; Hager, M. W.; El-Kattan, Y. A.; Liotta, D. C. *Synthesis*, **1995** *12*, 1465.
10. $^1J_{1,2}$ for α -D-arabinofuranose = 1-1.3 Hz; $^1J_{1,2}$ for β -D-galactofuranose < 1 Hz (due to broad singlet); $^1J_{1,2}$ for α -L-rhamnopyranose = 1.5 Hz, $^1J_{CH}$ for α -L-rhamnopyranose = 170.8 Hz, were observed in these compounds.
11. (a) Veltry, R.; Benvegnu, T.; Gelin, M.; Privat, E.; Plusquellec, D. *Carbohydr. Res.* **1997**, *299*, 7. (b) Bebault, G. M.; Dutton, G. G. S. *Can. J. Chem.* **1972**, *50*, 3373.