Acta Chemica Scandinavica B 35 (1981) 631–633

Silver Imidazolate-assisted Glycosidation. Part 3.* Synthesis of α-D-Glucopyranosides and α-D-Galactopyranosides

PER J. GAREGG, CARMEN ORTEGA and BERTIL SAMUELSSON

Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm, S-106 91 Stockholm, Sweden

Silver imidazolate together with mercury(II) chloride in dichloromethane is an efficient promoting system for glycosidations using the stable 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl and α-D-galactopyranosyl chlorides. This glycosidation promotor is useful for the synthesis of α-D-gluco- and α-D-galactopyranosides of sterically hindered alcohols.

For a long time, the synthesis of 1,2-*cis*-glycopyranosides remained a challenge in carbohydrate chemistry. Early on it was realized that protected β-D-glucopyranosides could be isomerized with Lewis acid to the more stable α-anomers [1] and that 1,2-*cis*-glycosides were sometimes formed in Koenigs-Knorr glycosidations,[2] but it was not until the concept of the neccessity for a non-participating group at C-2 was introduced,[2] in particular the benzyl group,[3] that stereospecific syntheses of 1,2-*cis*-glycosides came within reach. In recent years, the halide ion catalyzed glycosidation method of Lemieux and co-workers [4] has found wide-spread application and also the imidate procedure of Sinaÿ and co-workers.[5] Both these methods use 2,3,4,6-tetra-*O*-benzylhexosyl intermediates for glycosidations.

We have previously described silver imidazolate[6] – mercury(II) chloride promoted iodoalkoxylation of acetylated glycals. This gives 2-deoxy-2-iodo-α-D-hexopyranosides with 1,2-*trans*-configuration in good yields.[7,8] In the present and following papers we describe some further characteristics of silver imidazolate-assisted glycosidations. 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl and α-D-galactopyranosyl chlorides are allowed to react, in dichloromethane, with the appropriate alcohol in the presence of silver imidazolate and mercury(II) chloride. The addition of tetrabutylammonium chloride [9] greatly enhances the reaction rate, but does not affect the product distribution.

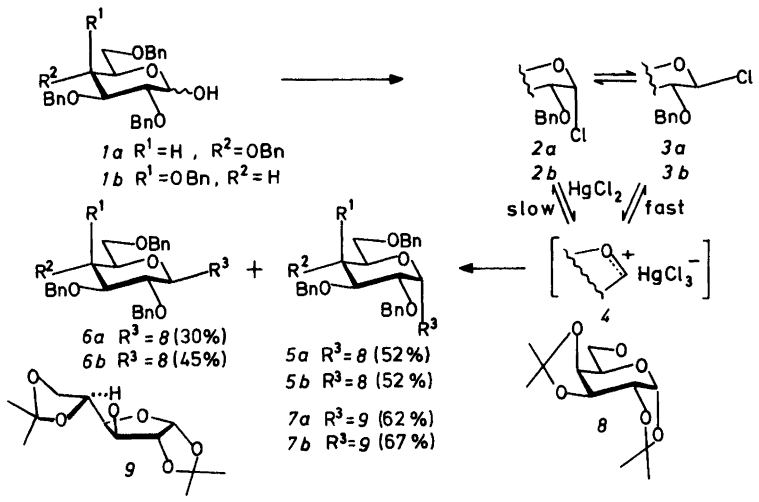
Silver imidazolate does not react with mercury(II) chloride or tetrabutylammonium chloride to any appreciable extent during the reaction. It remains insoluble, but readily reacts with any halogen acid produced in the reaction. In Koenigs-Knorr glycosidations, insoluble silver salts often have catalytic effects on the reaction.[2] However, in the present glycosidations no reaction took place unless a Lewis acid such as mercury(II) chloride was added. In reactions using mercury(II) chloride in the absence of silver imidazolate, rapid degradation of the reactants occurred. When, however, silver imidazolate and mercury(II) chloride were used together, a smooth reaction occurred, without degradation or hydrolysis of starting materials or products.

The addition of 1.4 mol equivalents of tetrabutylammonium chloride [9] to the reaction did not appear to alter the product composition, but gave a considerable enhancement of the reaction rate. This is different from the results obtained by Mattok and Phyllis [10] who in mercury(II) chloride-promoted alcoholyses of acylglycosyl halides found that the addition of lithium chloride decreased the reaction rate as part of the mercury(II) chloride was transformed into the $HgCl_3^-$ anion. This obviously is unimportant in the present glycosidations.

The results obtained are outlined in Fig. 1. Two alcohols of widely different steric accessibility were used, namely 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose and 1,2:5,6-di-*O*-isopropylidene-α-D-

* Parts 1 and 2 are Refs. 7 and 8.

0302-4369/81/090631-03$02.50



Scheme 1.

glucofuranose. The addition of chloride ion establishes an equilibrium between *2* (a or b) and *3* (a or b). It is suggested that the enhancement of reaction rate is explained by reaction of mercury(II) chloride with both anomeric chlorides giving a common ionic intermediate *4*, most easily formed from the more reactive β-chloride *3* (a or b). The product obtained from *4* depends upon the steric accessibility of the alcohol. A highly hindered alcohol will tend to give the α-D-glycoside.[11] The present glycosidation method thus gives the highest stereospecificity with sterically hindered alcohols.

In traditional work-up procedures of glycosidations using mercury salts, the latter are generally removed by extracting an organic phase of the product with aqueous potassium iodide. We found it difficult to extract all the mercury salts by this procedure and the last traces were therefore removed by treatment with aqueous sodium sulfide.

In an attempt to increase the specificity in glycosidation with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, mercury(II) chloride was replaced by zinc chloride, a Lewis acid promotor which also is compatible with silver imidazolate. A clean reaction took place, leading to an almost quantitative yield of the 1,2-*trans*-glycoside. Negligible amounts of the desired 1,2-*cis*-glycoside were obtained.

EXPERIMENTAL

General methods were the same as those reported elsewhere.[12]

Silver imidazolate.[6] A mixture of sodium hydroxide (14.7 g), silver nitrate (62.3 g) and imidazole (25.0 g) in water (1 l) was stirred in the dark at room temperature for 24 h. The white precipitate was filtered, washed with water, ethanol and acetone and then dried. Yield 62.2 g, (97 %).

Glycosidation procedure. *N,N*-Dimethylformamide (0.5 ml) in carbon tetrachloride (5 ml) was added to a suspension of phosphorus pentachloride (1.4 g) in carbon tetrachloride (50 ml). After stirring at room temperature for 40 min, the white precipitate was filtered off, washed with carbon tetrachloride and then added at room temperature to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-galactose (or -glucose)[13,14] (1.08 g, 2.0 mmol) in dichloromethane (20 ml). After 1 h, TLC (toluene–ethyl acetate 4:1) indicated complete reaction. The reaction mixture was diluted with dichloromethane (75 ml), washed with aqueous sodium hydrogencarbonate (4 × 50 ml), followed by water (2 × 50 ml), dried (Na_2SO_4), filtered and concentrated. The crude chlorides (*2a*, *2b*),[3,5,15–17] dissolved in dichloromethane (5 ml) were each added in the near-dark at room temperature to a stirred mixture of the appropriate di-*O*-isopropylidene hexose (*8* or *9*, 0.26 g, 1.0 mmol), mercury(II) chloride (1.08 g, 4.0 mmol), silver imidazolate (0.35 g, 2.0 mmol) and 3 Å molecular sieves in dichloromethane (10 ml). After 15 min, tetrabutylammonium chloride (0.39 g, 1.4 mmol) was added. After stirring at room temperature for 24 h in the dark the reaction was generally complete (TLC). If not, the mixture was stirred for another

2 h at 35 °C. The reaction mixture was filtered, the solids were washed with dichloromethane and the combined filtrates were washed with, in turn, aqueous potassium iodide, aqueous sodium hydrogencarbonate and then stirred with water containing excess sodium sulfide for 1 h, washed with water, dried (Na_2SO_4), filtered and concentrated. The products were purified by silica gel column chromatography (toluene – ethyl acetate 6:1).

6-O-(Tetra-O-benzyl-α-D-glucopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose[4] (5a). $[\alpha]_D^{22}$ +11° (*c* 1.3, chloroform). Lit.[4] $[\alpha]_D^{24}$ +10° (chloroform), δ_{13C} ($CDCl_3$): 96.2 (C-1), 97.0 (C-1'), 108.5, 109.1 [2 × *C* $(CH_3)_2$].

6-O-(Tetra-O-benzyl-β-D-glucopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (6a). $[\alpha]_D^{22}$ −22° (*c* 1.4, chloroform), δ_{13C} ($CDCl_3$): 96.3 (C-1), 104.3 (C-1'), 108.4, 109.2 [2 × *C*$(CH_3)_2$]. *Anal.* $C_{46}H_{54}O_{11}$: C, H.

6-O-(Tetra-O-benzyl-α-D-galactopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (5b). $[\alpha]_D^{22}$ +2° (*c* 0.9, chloroform), δ_{13C} ($CDCl_3$): 96.2 (C-1), 97.5 (C-1'), 108.4, 109.1 [2 × *C*$(CH_3)_2$]. *Anal.* $C_{46}H_{54}O_{11}$: C, H.

6-O-(Tetra-O-benzyl-β-D-galactopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (6b). $[\alpha]_D^{22}$ −94° (*c* 3.5, chloroform), δ_{13C} ($CDCl_3$): 96.5 (C-1), 102.4 (C-1'), 108.8, 109.5 [2 × *C*$(CH_3)_2$].

3-O-(Tetra-O-benzyl-α-D-glucopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose[4] (7a). $[\alpha]_D^{22}$ +43° (*c* 2.0, chloroform). [Lit.[4] $[\alpha]_D^{22}$ +46° (chloroform)]. δ_{13C} ($CDCl_3$): 97.7 (C-1'), 104.9 (C-1), 108.7, 111.5 [2 × *C*$(CH_3)_2$]. A small amount of the corresponding β-linked disaccharide (< 5 %) was isolated δ_{13C} ($CDCl_3$): 100.8 (C-1'), 104.6 (C-1), 108.0, 111.2 [2 × *C*$(CH_3)_2$].

3-O-(Tetra-O-benzyl-α-D-galactopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose[5] (7b). $[\alpha]_D^{22}$ +32° (*c* 1.0, chloroform). [Lit.[5] $[\alpha]_D^{22}$ +33° (chloroform)] δ_{13C} ($CDCl_3$): 98.9 (C-1'), 105.2 (C-1), 109.1, 111.2 [2 × *C*$(CH_3)_2$].

Glucosylation of 8 *using silver imidazolate and zinc chloride.* Dry zinc chloride was prepared by melting zinc chloride in a Pyrex glass tube over a gas flame. Heating was maintained until the vigorous boiling had ceased after which the remainder was poured into carbon tetrachloride. The pellets thus formed were powdered under dichloromethane before use and weighed without drying. The glycosyl chloride *2a* (0.84 g, 1.5 mmol) in dichloromethane (5 ml) was added in the near-dark at room temperature to a stirred mixture of *8* (0.26 g, 1.0 mmol), zinc chloride (0.8 – 1.0 g, 6 – 8 mmol), silver imidazolate (0.35 g, 2 mmol) and 3 Å molecular sieves in dichloromethane (15 ml). After 15 min, tetrabutylammonium chloride (0.42 g, 1.5 mmol) was added. The reaction was complete after 24 h. The reaction mixture was filtered, the solids were washed with dichloromethane and the combined filtrates were diluted with excess toluene. The solution was washed with aqueous sodium carbonate and water, dried ($MgSO_4$), filtered, concentrated and the product was purified by silica gel column chromatography (toluene – ethyl acetate 6:1). A yield of 0.765 g (98 %) of *6a* was obtained.

Acknowledgements. We are indebted to Professor Bengt Lindberg for his interest, to the Swedish Natural Science Research Council for financial support, to CONACYT, Mexico for a maintenance grant to C.O. and to the Royal Academy of Science (Stipendium Berzelianum) for a maintenance grant to B.S.

REFERENCES

1. Lindberg, B. *Acta Chem. Scand. 3* (1949) 1355.
2. Bochkov, A. F. and Zaikov, G. E. *Chemistry of the O-Glycosidic Bond*, Pergamon, Elmsford, Oxford 1979 and references therein.
3. Austin, P. W., Hardy, F. E., Buchanan, J. G. and Baddiley, J. *J. Chem. Soc.* (1964) 2128.
4. Lemieux, R. U., Hendriks, K. B., Stick, R. V. and James, K. *J. Am. Chem. Soc. 97* (1975) 4056.
5. Pougny, J. R., Jacquinet, J. C., Duchet, M. N. D., Milat, M. L. and Sinaÿ, P. *J. Am. Chem. Soc. 99* (1977) 6762.
6. Wyss, G. *Ber. Dtsch. Chem. Ges. 10* (1877) 1365.
7. Garegg, P. J. and Samuelsson, B. *Carbohydr. Res. 84* (1980) C1.
8. Garegg, P. J., Konradsson, P., Kvarnström, I., Samuelsson, B. and Svensson, S. C. T. *Carbohydr. Res. 92* (1981) 157.
9. Brändström, A. *Preparative Ion Pair Extraction*, Apotekarsocieten and Hässle Läkemedel, Stockholm, Hässle 1976, p. 144.
10. Mattok, G. L. and Phyllis, G. O. *J. Chem. Soc.* (1956) 1836.
11. Lemieux, R. U. *Chem. Soc. Revs. 7* (1978) 423.
12. Garegg, P. J., Hultberg, H. and Lindberg, C. *Carbohydr. Res. 83* (1980) 157.
13. Glaudeman, C. P. J. and Fletcher, H. G., Jr. *Methods Carbohydr. Chem. 6* (1972) 373.
14. Koto, S., Morishima, N., Miyata, Y. and Zen, S. *Bull. Chem. Soc. Jpn. 49* (1976) 2639.
15. Austin, P. W., Hardy, F. E., Buchanan, J. G. and Baddiley, J. *J. Chem. Soc.* (1965) 1419.
16. Jacquinet, J. C. and Sinaÿ, P. *Tetrahedron 35* (1979) 365.
17. Bosshard, H. H., Mory, R., Schmid, M. and Zollinger, H. *Helv. Chim. Acta 42* (1959) 1653.

Received July 28, 1981.