Carbohydrate Research, 162 (1987) 141-144
Elsevier Science Publishers B.V., Amsterdam - Printed in The Netherlands

Note

An improved synthesis of 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (levoglucosan triacetate)

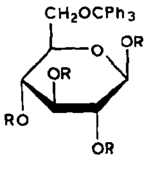
MOTHE VAMAN RAO AND MADHAVARAO NAGARAJAN*
School of Chemistry, University of Hyderabad, Central University P.O., Hyderabad 500 134 (India)

(Received August 13th, 1985; accepted for publication, November 3rd, 1986)

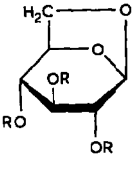
1.6-Anhydro-β-D-glucopyranose (levoglucosan, **2a**) and its derivatives, which are useful chiral synthons in the synthesis of biologically active molecules[1-4], have been synthesised by the pyrolysis of starch[5], treatment of phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside with alkali[6], and intramolecular displacement of a leaving group at the primary position[7,8]. A better yield of levoglucosan can be achieved by replacement of PhO-1 by either a pentachlorophenyl[9] or a pentabromophenyl group[10] and by the use of tetrabutylammonium hydroxide.

Levoglucosan triacetate (**2b**) has been obtained by treating 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose[11] with stannic chloride[12], zinc chloride[13], or toluene-*p*-sulfonic acid[14], and 1,2,3,4-tetra-*O*-acetyl-6-*O*-triphenylmethyl-β-D-glucopyranose (**1**) with zinc chloride[13] or allyl perchlorate[15]. Selective tosylation of D-glucose at HO-6 followed by treatment with base also gives levoglucosan[10].

In a systematic study of the cyclisation of **1** using various Lewis acids (Table I), the best yields (95 and 92%, respectively) of **2b** were obtained with anhydrous stannic chloride or anhydrous titanium(IV) chloride. On a 10-mmol scale using anhydrous stannic chloride, a slightly lower yield (83%) of **2b** was obtained. The reaction of stannic chloride with 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose has been reported[12] to give 40% of levoglucosan triacetate.



1 R = Ac



2a R = H
2b R = Ac

0008-6215/87/$03.50

TABLE I

CYCLISATION OF **1** TO **2b**, USING VARIOUS LEWIS ACIDS

Lewis acid	*Molar ratio of* **1** *to Lewis acid*	*Yield of* **2b** (%)
$SnCl_4$	1:2.5	95
$TiCl_4$	1:2.5	92
$ZrCl_4$	1:2.5	61
$AlCl_3$	1:3	40[a]
$BF_3 \cdot Et_2O$	1:2.5	26
$ZnCl_2$[13]	1:2.5	35
Allyl perchlorate[15]	1:3	29

[a] Based on **1** recovered.

A preparative scale reaction on a 0.1-mol scale, using anhydrous titanium(IV) chloride, gave an average yield of 78%, based on three runs. As the yields were comparable between stannic chloride and titanium(IV) chloride, the latter was preferred due to its lower cost.

As **1** can be obtained from D-glucose in high yield[11], the overall conversion of D-glucose into **2b** can also be achieved in high yield. A comparison of the existing methods for the conversion of D-glucose into **2b** with that of the procedure reported here is given in Table II. The present method involves only two steps from D-glucose and affords **2b** in yields superior to those of the methods reported earlier on a 0.1-mol scale and does not need any expensive reagents.

TABLE II

COMPARISON OF METHODS FOR THE CONVERSION OF D-GLUCOSE INTO **2b**

Number of steps involved from D-*Glucose*	*Scale on which* **2b** *was isolated (g)*	*Overall yield from* D-*Glucose* (%)	*Ref.*
[a]	75	18.8	5
3	275–300	26.6–34	6
2	20	28	7
3	43	31.8–33.8	9
3	0.92	39–41.4	10
2	1.97[b]; 0.95[c]	62; 30	10
3	0.3	28	12
2	1.6	27.1	13
3	0.550	3.5	14
2	0.57	25	15
2	2.39	72.5	[d]
2	22.46	67.8	[d]

[a] Starch pyrolysis. [b] Purified by column chromatography. [c] Direct crystallisation. [d] This work.

EXPERIMENTAL

Melting points were determined with a Büchi 510 apparatus and are uncorrected. Optical rotations were measured at 25° using a Rudolph Autopol II polarimeter. Column chromatography was performed on silica gel (100–200 mesh, Acme Synthetic Chemicals), using ethyl acetate and hexane. 1,2-Dichloroethane and titanium(IV) chloride were distilled from P_2O_5 and CaH_2, respectively, prior to use.

General procedure. — The appropriate Lewis acid was added to a solution of 1,2,3,4-tetra-*O*-acetyl-6-*O*-triphenylmethyl-β-D-glucopyranose { **1**, 1 mmol; m.p. 166–167°, $[\alpha]_D$ +45° (*c* 9, pyridine), prepared[11] from D-glucose (85.7% yield) } in 1,2-dichloroethane (10 mL). The mixture was stirred at 25° for 12 h, then poured into cold, saturated aqueous sodium hydrogencarbonate, and extracted with ethyl acetate (2 × 50 mL). The combined extracts were washed with water (50 mL) and aqueous sodium chloride, dried ($MgSO_4$), and concentrated *in vacuo*. Elution of the residue from a column (1.5 × 30 cm) of silica gel gave levoglucosan triacetate, m.p. 108–109°, $[\alpha]_D$ −60° (*c* 0.2, ethanol); lit.[5,6] m.p. 108–109°.

Preparative scale procedure: — To a stirred solution of **1** (59 g, 0.1 mol) in 1,2-dichloroethane (1 L) at −20° under nitrogen was added titanium(IV) chloride (47.42 g, 0.25 mol) at such a rate that the reaction temperature was maintained below −5°. When the addition was complete, the mixture was allowed to attain room temperature and stirring was continued for 24 h. The mixture was then poured slowly into cold, saturated, aqueous sodium hydrogencarbonate (800 mL), the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 200 mL). The combined organic layers were washed with water (2 × 350 mL) and then aqueous sodium chloride, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was adsorbed on to silica gel (50 g), loaded on to a column of silica gel (450 g), and eluted with ethyl acetate–hexane (25:75) to give levoglucosan triacetate (21.8–22.9 g, 76–79.6%).

ACKNOWLEDGMENT

This research was supported by the University Grants Commission in the form of a Special Assistance Programme in Organic Chemistry to the School of Chemistry.

REFERENCES

1 M. Černý and J. Staněk, Jr., *Adv. Carbohydr. Chem. Biochem.*, 34 (1977) 23–177.
2 T. Ogawa, T. Kawano, and M. Matsui, *Carbohydr. Res.*, 57 (1977) c31–c35.
3 A. G. Kelly and J. S. Roberts, *J. Chem. Soc., Chem. Commun.*, (1980) 228–229.
4 J. N. Freskos and J. S. Swenton, *J. Chem. Soc., Chem. Commun.*, (1985) 658–659.
5 R. B. Ward, *Methods Carbohydr. Chem.*, 2 (1963) 394–396.
6 G. H. Coleman, *Methods Carbohydr. Chem.*, 2 (1963) 397–399.
7 M. Akagi, S. Tejima, and M. Haga, *Chem. Pharm. Bull.*, 10 (1962) 905–909.
8 H. J. Jennings and J. K. N. Jones, *Can. J. Chem.*, 43 (1965) 2372–2386.

9 I. Fujimaki, Y. Ichikawa, and H. Kuzuhara, *Carbohydr. Res.*, 101 (1982) 148–151.

10 M. Kloosterman, M. J. Dees, G. A. van der Marel, and J. H. van Boom, *Recl. Trav. Chim. Pays-Bas*, 104 (1985) 116–119.

11 R. L. Whistler, L. W. Doner, and M. Kosik, *Methods Carbohydr. Chem.*, 6 (1972) 411.

12 R. U. Lemieux and C. Brice, *Can. J. Chem.*, 30 (1952) 295–310.

13 H. Bredereck and G. Hoschele, *Chem. Ber.*, 86 (1953) 1286–1294.

14 D. McGrath, E. E. Lee, and P. S. O'Colla, *Carbohydr. Res.*, 11 (1969) 453–460.

15 V. A. Nesmeyanov, S. E. Zurabyan, and A. Ya. Khorlin, *Tetrahedron Lett.*, (1973) 3213–3216.