Carbohydrate Research, 77 (1979) 262–266

Note

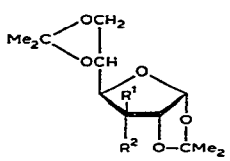
Carbohydrate triflates: reactions with bases

THOMAS W. FLECHTNER
Chemistry Department, Cleveland State University, Cleveland, Ohio 44115 (U.S.A.)
(Received November 3rd, 1978; accepted for publication in revised form, April 15th, 1979)

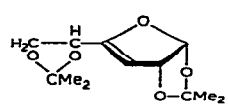
A number of reports[1–13] have appeared describing the reactions of trifluoromethanesulfonate (triflate) derivatives of carbohydrates. Substitution is generally observed, except for one instance in which elimination took place[6]. This report describes results concerning the interaction of carbohydrate triflates with bases.

Treatment of 1,2:5,6-di-*O*-isopropylidene-3-*O*-triflyl-α-D-glucofuranose[4] (**1**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry ether at room temperature afforded, after conventional isolation, crystalline 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**2**) in 98% yield, based on the glucofuranose **3** from which **1** had been prepared. The reaction of **1** with a slurry of potassium *tert*-butoxide in ether gave **2** in 67% yield. The latter process is similar to that reported by Srivastava[14] in which the reaction of the 3-*p*-toluenesulfonate analogue of **1** with potassium *tert*-butoxide in dimethyl sulfoxide afforded **2** in 69% yield. The *gluco* triflate **1** was unreactive at room temperature in the presence of ammonia at one atm.*.

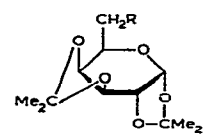
The reaction of 1,2:3,4-di-*O*-isopropylidene-6-*O*-triflyl-α-D-galactopyranose[4] (**4**) at room temperature with ammonia at one atm. gave a basic product that did



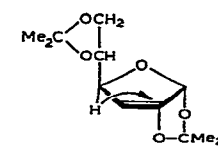
1 R^1 = OTf, R^2 = H
3 R^1 = OH, R^2 = H
8 R^1 = H, R^2 = OTf
9 R^1 = NHAc, R^2 = H
10 R^1 = NH_2, R^2 = H
11 R^1 = H, R^2 = OH



2



4 R = OTf
5 R = NH_2
6 R = NHAc
7 R = OH



12

Tf = CF_3SO_2

*The 3-*O*-tosyl analogue of **1** reacts with ammonia at elevated temperature and pressure[15].

not crystallize. This material was acetylated by the method of Szarek and Jones[16]. The basic material showed i.r. and ^{1}H-n.m.r. spectra superposable upon those of 6-amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[16] (**5**); in addition, spectra of the acetylated material similarly matched those of the 6-acetamido derivative[16] (**6**). The amide was isolated in 96% yield, based on the galactose derivative (**7**) from which **4** had been prepared. The amine **5** has been previously prepared by direct displacement on the 6-*O*-tosyl analogue of **3** with ammonia in a sealed-tube reaction[17,18].

1,2:5,6-Di-*O*-isopropylidene-3-*O*-triflyl-α-D-allofuranose[4] (**8**) did not react in the presence of DBU in ether at room temperature nor in boiling benzene overnight. When **8** was stirred with a slurry of potassium *tert*-butoxide in benzene for 3 days at room temperature, the hexenofuranose **2** was produced and isolated in 25% yield. When a small amount of a crown ether (18-crown-6) was added, the same conversion was almost complete in 0.5 h, but the yield was not increased.

The *allo* triflate **8** did not react with anhydrous ammonia at 1 atm pressure at room temperature, but it did react with a slurry of sodium amide in ether to afford an amine. This amine was acetylated and the acetamide was shown to be 3-acetamido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**9**) by comparison of its physical properties with those reported for **9** by Williams and Jones[19]. The amine was therefore 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**10**). The amide **9** was isolated in 32% yield, based on starting allose derivative **11**.

The elimination reaction of the *allo* triflate is formally a *syn* process. Although such reactions in five-membered ring compounds are reasonably well known[20], the extreme ease with which **1** underwent *anti* elimination suggested an alternative possibility for **8**. An *anti* elimination process with **8** would afford 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-2-enofuranose (**12**). Compound **12** should be highly strained, and might well isomerize to **2** rapidly.

The isomerization of **12** to **2** involves a formal 1,3-antarafacial hydrogen-shift (note structure **12**), a process that cannot be intramolecular[21]. If it occurs a solvent molecule must thus be involved in the formal transfer of the hydrogen. Specifically, solvent hydrogen would be incorporated at C-2 of the **2** formed.

The *allo* triflate **8** was treated with potassium *tert*-butoxide in benzene in the presence of *tert*-butyl alcohol-O-D. The ^{1}H-n.m.r. spectrum of the **2** produced showed a clear doublet for the anomeric proton, indicating that there had been no deuterium incorporation at C-2. Therefore **12** is not an intermediate in the production of **2** from **8**.

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. spectra were determined on a Varian T60 spectrometer in chloroform-*d* with tetramethylsilane as the internal standard. I.r. spectra were determined on a Beckman Acculab 1 instrument as thin films. Trifluoromethanesulfonic anhydride was prepared[22] from the acid, which was purchased

from 3M Co. Dichloromethane was distilled before use. Diethyl ether and benzene were distilled and stored over sodium ribbon; pyridine and *tert*-butyl alcohol were distilled and stored over 4A molecular sieves. The 18-crown-6, DBU, and *tert*-butyl alcohol-O-D were used as supplied by Aldrich. Solvents were removed *in vacuo*.

Carbohydrate triflates **1**, **4**, *and* **8**. — The three esters were prepared by a procedure that is a modification of those reported by Hall and Miller[3,4] and by Binkley and Hehemann[9]. To a stirred solution of triflic anhydride (1 mL) in dichloromethane (20 mL) at −10° to −15° (ice–acetone bath) was added pyridine (1 mL) in dichloromethane (10 mL) at such a rate that the temperature of the reaction stayed below −5°. When the addition of pyridine was complete, the solution was again cooled to −10° and then 1.0 g of the partially protected carbohydrate (**3**, **7** or **11**) in dichloromethane (10 mL) was added dropwise during 20 min. This solution was then stirred at −5 to −10° for 0.5 h and finally poured into ice–water (100 mL) containing sodium hydrogencarbonate (200 mg). This mixture was stirred until the ice melted and the layers then separated. The dichloromethane solution was washed with cold, 3% hydrochloric acid, water, and saturated sodium chloride. Solvent removal afforded the solid triflate in 90–100% yield. Triflates **1** and **8** could be recrystallized[4], but were usually used directly.

*Reactions of 1,2:5,6-di-*O*-isopropylidene-3-*O*-triflyl-α-*D*-glucofuranose* (**1**). — *A. With DBU.* To a solution of 697 mg (1.78 mmol) of **1** in dry ether (50 mL) was added 0.50 mL (510 mg, 3.4 mmol) of DBU. The resulting solution was stirred overnight at room temperature, during which time a brown oil appeared. This solution was washed with water, cold 3% hydrochloric acid, water again, and saturated sodium chloride solution, dried (magnesium sulfate) and the solvent removed to afford 421 mg (1.74 mmol, 98%) of **2**. This alkene had a ^{1}H-n.m.r. spectrum superposable on that of authentic* **2** and reported[8] for **2** and had m.p. 48–50° (lit.[8] m.p. 50–52°, and[23] 50°).

B. With potassium tert-*butoxide.* To a solution of 674 mg (1.72 mmol) of **1** in dry benzene (50 mL) was added 347 mg (3.10 mmol) of finely powdered potassium *tert*-butoxide. This slurry was stirred overnight, whereupon the mixture became dark brown. The benzene solution was washed with water (twice), saturated sodium chloride, and dried (sodium sulfate). Solvent removal afforded 277 mg (1.14 mmol, 67%) of **2**, m.p. 47–50°.

C. With ammonia. Anhydrous ammonia was slowly bubbled overnight into a solution of 1.561 g (3.98 mmol) of **1** in 50 mL of dry ether. Solvent removal afforded 1.565 g (100%) of recovered **1**.

*Reaction of 1,2:3,4-di-*O*-isopropylidene-6-*O*-triflyl-α-*D*-galactopyranose* (**4**) *with ammonia.* — Anhydrous ammonia was slowly bubbled overnight into a solution of 1.862 g (4.75 mmol) of **4** in chloroform (50 mL). This solution was then washed with water and saturated sodium chloride and the solvent removed to afford 1.258 g (4.86 mmol, 102%) of **5** as a clear glass; n.m.r. ($CDCl_3$): δ 5.45 (1 H, J 5 Hz, H-1),

*Kindly provided by Professor Roger W. Binkley of this University.

4.51 (1 H, *J* 7 and 2 Hz, H-3), 4.2–4.0 (3 H, H-2,4,5), 2.85 (2 H, H-6), 1.50, 1.42, 1.30 (12 H). The pattern observed was similar to those reported[24–26] for a number of 6-substituted 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose derivatives, and the assignments were made by analogy with those reports. A solution of this material in dry pyridine (5.0 mL) was cooled to 0°, redistilled acetic anhydride (2 mL) was added, and the solution was stirred for 2 days at room temperature. Conventional processing afforded **6** as a clear glass*; ^{1}H-n.m.r. ($CDCl_3$): δ 5.53 (1 H, *J* 5 Hz, H-1), 4.63 (1 H, *J* 7, 2 Hz, H-3), 4.55–3.60 (5 H, H-2,4,5,6), 2.08 (3 H, $COCH_3$), and 1.52, 1.45, 1.33 (12 H). The n.m.r. and i.r. spectra of **5** and **6** prepared in this way were superposable upon those of **5** and **6** prepared by the procedure of Szarek and Jones[16].

*Reactions of 1,2:5,6-di-*O*-isopropylidene-3-*O*-triflyl-α-D-allofuranose* (**8**). — *A. With DBU, ammonia, and potassium* tert*-butoxide.* A solution of 1.050 g (2.68 mmol) of **8** and 1.0 g (6.6 mmol) of DBU in dry benzene (50 mL) was boiled for 20 h under reflux under a nitrogen atmosphere. Conventional processing provided 883 mg (84%) of recovered **8**. Ammonia was bubbled through a solution of 881 mg (2.47 mmol) of **8** in dichloromethane (50 mL) for 20 h at room temperature. Removal of solvent afforded 823 mg (93%) of **8**. To a solution of 792 mg (2.02 mmol) of **8** in dry benzene (50 mL) was added 2.24 g (20.0 mmol) of potassium *tert*-butoxide. This slurry was stirred for 3 days at room temperature with a drying tube installed on the flask. A simple isolation afforded 122 mg (0.504 mmol, 25%) of **2**. Reactions conducted similarly for shorter times afforded mixtures of **2** and **8** (analyzed by n.m.r. spectroscopy). When 18-crown-6 (278 mg, 1.05 mmol) was added to a slurry of 1.233 g (3.15 mmol) of **8** in dry benzene (50 mL) and 1.091 g (9.8 mmol) of potassium *tert*-butoxide, the mixture immediately turned black. After 0.5 h, the mixture was diluted with 100 mL of water and the water-insoluble material isolated to give 485 mg of a mixture of **8** and **2** (~1:2 by n.m.r. analysis).

To a solution of 1.583 g (4.04 mmol) of **8** in dry benzene (50 mL) containing 5.0 g (67 mmol) of *tert*-butyl alcohol-O-D was added 2.363 g (21.1 mmol) of potassium *tert*-butoxide. After 15 h, this slurry had turned black. After a total of 17 h, the mixture was poured into water, the organic phase was separated, and it was washed several times with water and then with saturated sodium chloride solution, dried (sodium sulfate), and the solvent removed to afford 301 mg of **2** contaminated with some starting material. The ^{1}H-n.m.r. spectrum of this material showed a clear doublet for H-1.

B. With sodium amide. To a solution of 1.230 g (3.14 mmol) of **8** in dry ether (50 mL) was added 2.0 g (51.3 mmol) of sodium amide. The flask was equipped with a drying tube and the solution was stirred for 2 days at room temperature. The brown slurry was then poured into water (100 mL), the organic phase washed with water and saturated sodium chloride solution, and the solvent removed to afford 972 mg of a brown semi-solid. The ^{1}H-n.m.r. spectrum of this material showed it to be a mixture (there were several anomeric-proton absorptions for example), but it was

*Compound **6** has been reported[27] as a solid, but we have been unable to crystallize this compound.

soluble in 3% aqueous hydrochloric acid. Acetylation as before afforded 301 mg (1.00 mmol, 32%) of **9**, m.p. 60°; recrystallized from methanol–water it had m.p. 79–80° (lit.[19] m.p. 76–77°); n.m.r. ($CDCl_3$): δ 5.73 (1 H, multiplet, H-1), 5.00–4.67 (2 H, multiplet), 4.43–3.63 (5 H, multiplet), 2.10 (3 H, singlet, $COCH_3$), and 1.53, 1.38, 1.33 (12 H).

ACKNOWLEDGMENTS

The College of Graduate Studies of Cleveland State University is thanked for its support of this work. Special appreciation is expressed to Professor Roger W. Binkley.

REFERENCES

1 F. J. Kronzer and C. Schuerch, *Carbohydr. Res.*, 27 (1973) 379–390.
2 A. Maradufu and A. S. Perlin, *Carbohydr. Res.*, 32 (1974) 261–277.
3 L. D. Hall and D. C. Miller, *Carbohydr. Res.*, 40 (1975) C1–C2.
4 L. D. Hall and D. C. Miller, *Carbohydr. Res.*, 47 (1976) 299–305.
5 T. H. Haskell, P. W. K. Woo, and D. R. Watson, *J. Org. Chem.*, 42 (1977) 1302–1305.
6 R. Ranganathan, *Tetrahedron Lett.*, (1977) 1291–1294.
7 V. Marousek, T. J. Lucas, P. E. Wheat, and C. Schuerch, *Carbohydr. Res.*, 60 (1978) 85–96.
8 T. J. Tewson and M. J. Welch, *J. Org. Chem.*, 43 (1978) 1090–1092.
9 R. W. Binkley and D. G. Hehemann, *J. Org. Chem.*, 43 (1978) 3244–3245.
10 R. Ranganathan and D. Larwood, *Tetrahedron Lett.*, (1978) 4341–4344.
11 L. Foley, J. T. S. Lin, and M. Weigele, *J. Antibiot.*, 31 (1978) 979–984.
12 J. Leroux and A. S. Perlin, *Carbohydr. Res.*, 67 (1978) 163–178.
13 A. S. Perlin, *Pure Appl. Chem.*, 50 (1978) 1401–1408.
14 H. C. Srivastava and V. K. Srivastava, *Carbohydr. Res.*, 60 (1978) 210–218.
15 K. Freudenberg, O. Burkhart, and E. Braun, *Ber.*, 59 (1926) 714–720.
16 W. A. Szarek and J. K. N. Jones, *Can. J. Chem.*, 43 (1965) 2345–2356.
17 K. Freudenberg and A. Doser, *Ber.*, 58 (1925) 294–300.
18 V. I. Veksler, *Zh. Obshch. Khim.*, 31 (1961) 989–993.
19 D. T. Williams and J. K. N. Jones, *Can. J. Chem.*, 45 (1967) 7–9.
20 W. H. Saunders, Jr., and A. F. Cockerill, *Mechanisms of Elimination Reactions*, Wiley, New York, 1973, pp. 124–136.
21 R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1971, p. 118.
22 M. Fieser and L. F. Fieser, *Reagents for Organic Synthesis*, Vol. 4, Wiley, New York, 1974, p. 533.
23 H. Zinner, G. Wulf, and R. Heinatz, *Chem. Ber.*, 97 (1964) 3536–3540.
24 C. Cone and L. Hough, *Carbohydr. Res.*, 1 (1965) 1–9.
25 D. Horton and H. S. Prihar, *Carbohydr. Res.*, 4 (1967) 115–125.
26 L. Evelyn and L. D. Hall, *Carbohydr. Res.*, 47 (1976) 285–297.
27 H. Saeki, T. Iwashige, E. Ohki, K. Furuya, and M. Shirasaka, *Ann. Sankyo Res. Lab.*, 19 (1967) 137–143; *Chem. Abstr.*, 68 (1968) 96075f.