Tetrahedron Letters No.30, pp. 2825-2828, 1971. Pergamon Press. Printed in Great Britain.

BORON TRIFLUORIDE-CATALYZED ACETOLYSIS OF GLYCOSIDES

F.W. Lichtenthaler, J. Breunig, and W. Fischer

Institut für Organische Chemie, Technische Hochschule Darmstadt
61 Darmstadt (Germany)

(Received in UK 7 June 1971; accepted in UK for publication 24 June 1971)

Various reactions at the anomeric centre of acetylated sugars have been shown to be catalyzed by boron trifluoride, which was utilized as such in chloroform solution, or in form of its etherreal, anisol or acetic acid complex in solvents such as benzene, acetic acid or acetic anhydride. Thus ß→α-rearrangements of alkyl glycoside peracetates[1] and anomerizations of penta-O-acetyl-D-glucopyranoses[2] are readily evoked by BF_3 as well as conversions of aldose peracetates into aryl glycosides[3], nucleosides[4], and dithioacetal derivatives[5]. Reactions involving a BF_3-catalyzed acetolysis of glycosides have apparently not been disclosed, which is somewhat unexpected, since the use of acetic anhydride in the presence of BF_3-etherate has recently been advocated for O-acetylating methyl glycosides of certain nitro and acetamido-nitro sugars without affecting glycoside or benzylidene acetal structures[6]. The results presented below demonstrate, that in the case of aldohexosides and hexulosides either O-acetylation or acetolysis or both can be effected with acetic anhydride in the presence of BF_3-etherate, whereas with methyl pentosides rupture of the pyranoside ring is observed to yield acyclic products[x].

Thus, when methyl α-D-xylopyranoside (1) or its tri-O-acetyl derivative (2) is treated with acetic anhydride containing a few drops of BF_3-etherate (4 hrs. at 0° or 1 hr. at ambient temperature), an approximate 1:1-mixture of the 1-O-methyl-1, 2, 3, 4, 5-penta-O-acetyl-aldehydo-D-xyloses with 1S (3) and 1R (4) configuration is obtained, which can be separated by elution from a silicagel column with cyclohexane/methanol (10:1). The isomer, eluted first, is obtained in 35 % yield as an analytically pure and chromatographically uniform sirup with $[\alpha]_D^{23}$ -4° (c 4, $CHCl_3$) and a 6.0 Hz-doublet for H-1 at 4.20 τ ($CDCl_3$), whereas the last fractions afforderd in a yield of 21 % the other isomer, also characterized as a sirup with $[\alpha]_D^{23}$ -0.8° and a doublet for H-1 with $J_{1,2}$ = 4.5 Hz at 4.20 τ. The intermediate fractions were devoid of pyranose derivatives, i.e. 6 or its anomer; only 3 and 4 could be detected by t.l.c.

x) All known compounds obtained herein hat physicochemical data in agreement with those in the pertinent literature; the others gave acceptable analyses and afforded n.m.r. spectra that were in accord with their structures.

1 R=H
2 R=Ac

3 R=Me, R'=Ac
4 R=Ac, R=Me

5

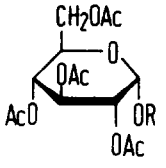
6

In acetic anhydride/BF_3-etherate, at 0° or at room temperature the acylic hemiacetals 3 and 4 are readily interconverted, again forming a mixture in approximately equal amounts. However, when subjected to higher temperatures in this medium (i.e. 12 hrs., at 60°), the methoxy group in 3 or 4 is acetolyzed to give in yields over 90 % hexa-O-acetyl-aldehydo-D-xylose 5, which due to its rather incommodious crystallization[7,8] was isolated as an analytically pure sirup of $[\alpha]_D^{25}$ + 4° (c 1, $CHCl_3$). The NMR-chracteristics resembled those of 3 and 4 except for an additional acetoxy resonance in the 8 τ region on expense of the methoxy signal (at 6.54 τ in 3 and 4) and a 5 Hz-doublet at 3.20 τ for H-1. The same acyclic hexaacetate (5) is obtained in equally good yields from 2 or 6 or, even more convenient, from D-xylose directly, when treated with acetic anhydride in the presence of BF_3-etherate at 50-60° for 8-10 hours.

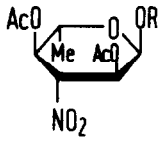
Similar to the results obtained in sulfuric acid catalyzed acetolyses[9-11], methyl aldohexopyranosides are much less readily acetolyzed by BF_3/acetic anhydride than their pentose analogues. Hence, the α-methyl glycosides of D-glucose, 3-nitro-3,6-dideoxy-L-glucose and D-mannose can safely be O-acetylated by BF_3-etherate/acetic anhydride (30-45 min. at 0-10°), to give the corresponding per-O-acetates 7, 9, m.p. 109-110°, $[\alpha]_D^{25}$ -154° (c 1, $CHCl_3$), and 11 in nearly quantitative yields. However, under more forcing conditions (3-10 hrs. at 40°), acetolysis is effected in each case. The glucoside 7, (10 hrs., 40°) yields the anomeric pentaacetyl-glucopyranoses in an α/ß-ratio of 85:15 (NMR in $CHCl_3$), from which crystalline 8 can be isolated in 75% yield; hepta-O-acetyl-aldehydo-D-glucose, a side product in acetolysis reactions of 7 with sulfuric or perchloric acid as the catalyst[12,13] could not be detected by t.l.c. or NMR in the motherliquor remaining after isolation of 8. The nitroglucoside 9 is acetolyzed unter these conditions (3 hrs. 40°) to give tri-O-acetyl-3-nitro-3,6-dideoxy-α-L-glucopyranose (10), m.p. 147-148°, $[\alpha]_D^{25}$ -118° (c 1, $CHCl_3$) in 76 % yield, the anomeric configurations clearly following from a 3.5 Hz-doublet at 3.62 τ for H-1 and acetoxy resonances at 7.83 (α-OAc), 7.92 and 8.00 τ in accord with the acetyl resonance rule[14].

As compared with the glucosides 7 and 9, BF_3-catalyzed acetolysis of methyl-tetra-O-acetyl-α-D-mannopyranoside (11) takes a much less uniform course. Under comparable conditions (10 hrs., 40°), a mixture of five components is obtained, consisting of the penta-O-acetyl-D-

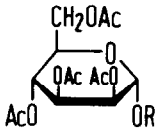
mannopyranoses in an approximate α/β-ratio of 7:1 (60 %), the C-1-epimeric methyl hemiacetals of hexaacetyl-aldehydo-D-mannose (13 and 14, respectively) in a 1:1 mixture (30 %), and of heptaacetyl-aldehydo-D-mannose (15) to an extent of 10 %. All constituents of this mixture can be isolated by elution from silicagel with cyclohexane-ethanol (10:1), rechromatography being required in the case of the methyl hemiacetals; their physicochemical data corresponded with those in the literature[7, 15]. The methyl hemiacetals 13 and 14 are readily interconverted by acetic anhydride/BF_3 at ambient temperature; on longer treatment (48 hrs., 40°), however, they quantitatively yield the acylic heptaacetate 15, suggesting that its formation from 11 proceeds via 13 and 14 as intermediates rather than other possible routes. Correspondingly, when 11 is subjected to BF_3/acetic anhydride for 48 hours at 40°, the resulting mixture is composed of 12, its β-anomer and 15 as the only acylic derivative, from which it can be isolated in 18 % yield.



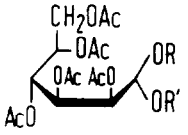
7 R=Me
8 R=Ac



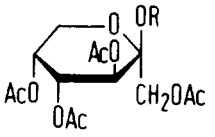
9 R=Me
10 R=Ac



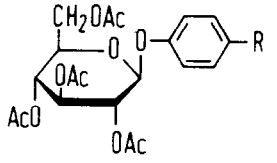
11 R=Me
12 R=Ac



13 R=Me, R'=Ac
14 R=Ac, R'=Me
15 R=R'=Ac



16 R=$C_6H_5CH_2$
17 R=Ac



18 R=H
19 R=Ac

Similar results are obtained with benzyl β-D-fructopyranoside. On reaction with BF_3/acetic anhydride (0°, 20 min.) it is readily converted to its tetra-O-acetyl derivative (16) in 82 % yield, whereas under slightly more forcing conditions (2. hrs., 25°) acetolysis occurs to give penta-O-acetyl-β-D-fructopyranose (17), isolable in 76 % yield. With phenyl tetra-O-acetyl-β-D-glucopyranoside (18), however, not only acetolysis to the usual anomeric mixture of penta-acetyl-D-glucoses is observed, but also C-acylation in the aromatic ring. Though 18 is completely acetolyzed when treated with acetic anhydride/BF_3 for 3 days at 60°, less rigid conditions (7 days, 37°) give mixtures, from which the known[16] p-acetylphenyl tetra-O-acetyl-β-D-glucopyranoside (19) can be isolated in a yield of 42 %. This formation of Friedel-Crafts acylation products seems to be a specific attribute of BF_3, since 19 cannot be detected in acetolysis mixtures obtained on catalysis with sulfuric or perchloric acid under conditions used previously[9, 13].

On treatment af adenosine with acetic anhydride/BF_3-etherate for 1-2 hours at room temperature, its tri-O-acetate can be isolated in yields of 73-75 % [17]. Our preliminary experiments indicate that parallel to O-acetylation acetolysis of the N-glycosidic linkage is observed, though at a slower rate; after 1.5 hours at 25°, about 10 % of the tri-O-acetyl-adenosine formed is acetolyzed to products originating from adenine and the sugar portion, which with progressing time steadily increase and constitute the only products detectable by t.l.c. after 3 days.

The foregoing results, though of purely preparative nature, seem to indicate that BF_3 as a catalyst in acetolysis reactions is a efficacious yet smoother than sulfuric or perchloric acid, showing a close resemblance to $ZnCl_2$ in its catalytic activity, particulary in relation to the acetolysis results on methyl ß-D-arabinoside [10]. Further studies directed toward BF_3-catalyzed acetolyses of other glycosides, especially those of aminosugars, are in progress.

Acknowledgements: Financial support from the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

---

1. B. Lindberg, Acta. Chem. Scand., 2, 534, 426 (1948); R. L. Whistler, K. A. Kimmel and D. F. Durso, J. Amer. Chem. Soc., 73, 3530 (1951).

2. Z. Csűrös and G. Deák, Acta. Chim. Hung., 19, 165 (1959); Z. Csűrös, G. Deák, and G. Varsanyi, ibid., 19, 181 (1959).

3. H. Bretschneider and K. Beran, Monatsh., 80, 262 (1949).

4. U. Niedballa and H. Vorbrüggen, Angew. Chem., 82, 449 (1970); Angew. Chem. Intern. Ed. Engl., 9, 461 (1970).

5. M. L. Wolfrom and T. E. Whitely, J. Org. Chem., 27, 2109 (1962); H. G. Fletcher, Jr. and H. W. Diehl, Carbohyd., Res., 17, 383 (1971).

6. H. H. Baer and T. Neilson, J. Org. Chem., 32, 1068 (1967); H. H. Baer, F. Kienzle and F. Rajabalee, Can. J. Chem., 46, 80 (1968); H. H. Baer and F. Rajabalee, Carbohyd. Res., 12, 24 (1970).

7. N. W. Pirie, Biochem. J., 30, 374 (1936).

8. R. L. Whistler, E. Heyne and J. Bachrach, J. Amer. Chem. Soc., 71, 1476 (1949).

9. R. M. Hann and C. S. Hudson, J. Amer. Chem. Soc., 56, 2465 (1934).

10. Edna M. Montgomery, R. M. Hann and C. S. Hudson, J. Amer. Chem. Soc., 59, 1124 (1937).

11. L. Asp and B. Lindberg, Acta Chem. Scand., 4, 1446 (1950).

12. K. Freudenberg and K. Soff, Chem. Ber., 70, 264 (1937).

13. H. Bredereck, A. Wagner, G. Hagelloch, and G. Faber, Chem. Ber., 91, 515 (1958).

14. F. W. Lichtenthaler, G. Bambach, and P. Emig, Chem. Ber., 102, 994 (1969).

15. M. L. Wolfrom, M. Konigsberg, and F. B. Moody, J. Amer. Chem. Soc., 62, 2343 (1940).

16. F. Mauthner, J. prakt. Chem., 85, 564 (1912); 88, 764 (1913); Edna M. Montgomery, N. K. Richtmyer, and C. S. Hudson, J. Amer. Chem. Soc., 64, 649 (1942).

17. F. J. M. Rajabalee, Angew. Chem., 83, 82 (1971); Angew. Chem. Intern. Ed. Engl., 10, 75 (1971).