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SYNTHESIS OF ULOSES BY THE OXIDATION WITH DIMETHYL SULFOXIDE-TRIFLUOROACETIC ANHYDRIDE

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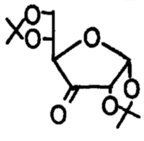
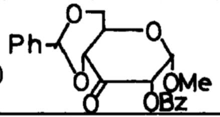
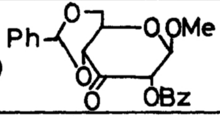
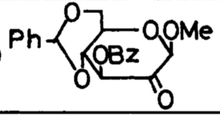
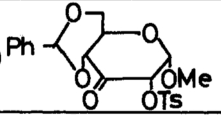
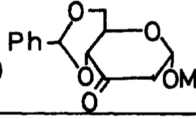
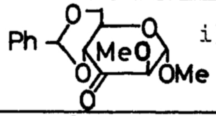
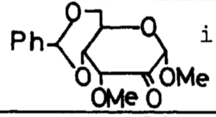
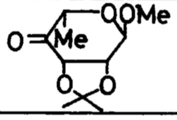
Application of dimethyl sulfoxide-trifluoroacetic anhydride for the oxidation of an isolated hydroxyl group of partially protected carbohydrates gave uloses in good yields, and for that of 2,3-dihydroxyl groups of D-glucosides followed by the reaction with carbonyl reagents gave easily 2,3-diulose derivatives.

Although the number of reports on the oxidation method is still increasing,[1-4] dimethyl sulfoxide(Me_2SO) oxidation[5] and its variations[6,7] have been widely used for the preparation of uloses: valuable intermediates in synthetic carbohydrate chemistry.[8,9] However, these methods are often accompanied with epimerization, elimination and the formation of by-products such as methylthiomethyl ether and others. Recently, Huang *et al.* reported that oxidation with Me_2SO-trifluoroacetic anhydride(TFAA) reagent is generally useful, operationally simple and highly effective for the conversion of sterically hindered alcohols to carbonyls.[10] This communication describes the application of this reagent for the oxidation of an isolated hydroxyl group or 2,3-dihydroxyl groups of carbohydrates.

The experiments have been carried out as follows: To a solution of dry Me_2SO (2 mmol) in distilled dry CH_2Cl_2(2 ml) cooled below -65°C with a dry ice-acetone bath was added dropwise TFAA(1.5 mmol) in CH_2Cl_2(0.5 ml) with stirring in *ca.* 10 min, and after 10 min, a solution of a partially protected sugar derivative(1 mmol) in CH_2Cl_2(2-3 ml) was subsequently added. The mixture was stirred below -65°C for 30 min, followed by addition of triethylamine(TEA, 0.4 ml) dropwise. The rate of addition of TFAA, sugar derivative and TEA was controlled to keep the temperature below -65°C. The cooling bath was then removed and the reaction mixture was

Table 1. Oxidation of an isolated hydroxyl group of carbohydrates

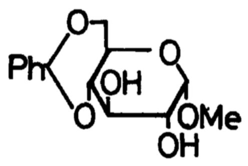
Products	Me$_2$SO-TFAA Yield, %	Me$_2$SO-Ac$_2$O(or others) Conditions Time, h (temp, °C)	Yield, % (methylthiomethyl ether, %)	CrO$_3$-pyridine or RuO$_4$ Yield, %
(1) 	84.8	18	62(20-30) 0-70(DCC)a) 45-65(P$_2$O$_5$)b)	6(CrO$_3$)c) 75-95(RuO$_4$)d)
(2) 	97.0	18 18(25-30)	52(2.6) 88(DCC, H$_3$PO$_4$)e)	
(3) 	98.2	18 18(25-30)	47.5(21.0) 90(DCC, H$_3$PO$_4$)e)	
(4) 	87.1	18 18	46.5(25.0) 90(DCC, H$_3$PO$_4$)e)	
(5) 	86.7	18(25-30) 1.5-2(65-70)	80(DCC, H$_3$PO$_4$)e) 85-92(P$_2$O$_5$)b)	
(6)  i)	89.0	18 60	70-90(~19) 90f)	53(CrO$_3$)f) 35(RuO$_4$)d)
(7)  i)	98.5	72	85(small quantity)	78(RuO$_4$)e)
(8)  i)	93.5	72	52(small quantity)	
(9) 	86.7	3-5(60)	81(P$_2$O$_5$)h)	34(CrO$_3$)g) 80-90(RuO$_4$)d)

a) G. H. Jones and J. G. Moffatt, *Methods Carbohyd. Chem.*, 6, 315 (1972); B. R. Baker and D. H. Buss, *J. Org. Chem.*, 30, 2304 (1965). b) J. S. Brimacombe, J. G.H. Bryan, A. Husain, M. Stacey, and M. S. Tolley, *Carbohyd. Res.*, 3, 318 (1967); K. Onodera, S. Hirano, and N. Kashimura, *carbohyd. Res.*, 6, 276 (1968). c) O. Theander, *Acta, Chem. Scand.*, 18, 2209 (1964). d) P. J. Beynon, P. M. Collins, P. T. Doganges, and W. G. Overend, *J. Chem. Soc. (C)*, 1966, 1131; D. C. Baker, D. Horton, and C. G. Tindall, Jr., *Carbohyd. Res.*, 24, 192 (1972). e) P. M. Collins, D. Gardiner, S. Kumar, and W. G. Overend. *J. Chem. Soc. Perkin I*, 1972, 2596. f) A. Rosenthal and P. Catsoulacos, *Can. J. Chem.*, 46, 2864 (1968). g) B. Flaherty, W. G. Overend, and N. R. Williams, *J. Chem. Soc. (C)*, 1966, 398. h) V. H. Parikh and J. K. N. Jones, *Can. J. Chem.*, 43, 3452 (1965). i) An axial hydroxy group of the starting material was oxidized in these cases, and an equatorial one in others.

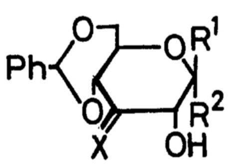
allowed to warm up to room temperature, washed with H_2O(5 ml) and the water layer was extracted with CH_2Cl_2. Usual work-up of the combined organic solutions gave an ulose, and the yield was estimated by densitometer and NMR analysis. As shown in Table 1, Me_2SO-TFAA method was widely applicable, and gave better results than hitherto known reagents at lower temperature in a shorter period. No epimerization occurred in the preparation of (8) [mp 113-116°C, $[\alpha]_D$ +69.8° (c 1.0, $CHCl_3$)], though only 3-epimer of 8 was obtained in 23% yield by the oxidation with CrO_3-pyridine.[11)]

On the other hand, it has been known that the direct oxidation of glycosides having vicinal hydroxyl groups with CrO_3-pyridine gave a mixture of monouloses in very low yields.[12)] Recently, it was reported that the oxidation of methyl 4,6-O-benzylidene-α-D-glucopyranoside (10) with Me_2SO-P_2O_5[13)] or Me_2SO-Ac_2O[14)] gave the corresponding mono-3-ulose (11a)[15)] or its 2-O-acetate in 11% and 24% yields, respectively, but not the corresponding 2,3-diulose (12a).

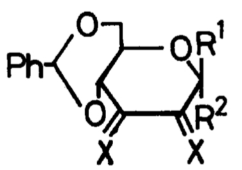
In our experiments, oxidation of 10 with Me_2SO-TFAA and the subsequent reaction of the crude product with phenylhydrazine and 1,2-diaminobenzene gave the bis(phenylhydrazone) (12b)[15)] and the quinoxaline derivative (13a)[16)] of 12a[17)] in 25% and 30% yields, respectively. Similar reactions of the β-anomer of 10 gave also the corresponding (12c) [mp 173-177°C, $[\alpha]_D$ +286° (c 1.2, $CHCl_3$), NMR(δ); 12.51 and 10.03 (2xNH), 7.64-6.71 (m, 3xPh), 5.77 (=CHPh), 5.30 (H_4; $J_{4,5}$ =9.0), 5.25 (H_1: s), 4.46 (H_{6e}; q, $J_{6e,5}$= 4.0), 3.85 (H_{6a}; t, $J_{6a,5}$=10.0), 3.47 (OMe)] and (13b) [mp 186-188°C, $[\alpha]_D$ -158° (c 0.74, $CHCl_3$), NMR: 8.3-7.3 (2xPh), 5.90 (CHPh). 5.86 (H_1; s), 5.26 (H_4; d, $J_{4,5}$= 8.0, $J_{4,6e}$= 2.0), 4.66-4.42 (H_{6e}; m), 4.12 (H_{6a}; t, $J_{6a,6e}$= $J_{6a,5}$= 9.5), *ca.* 4.10 (H_5; m), 3.68 (OMe)] in 20% and 25% yields, respectively. In order to disclose the intermediates for the formation of



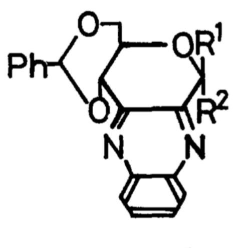
(10)



(11a) R^1=H, R^2=OMe, X=O
(11b) R^1=OMe, R^2=H, X=O
(11c) R^1=H, R^2=OMe, X=NNHPh
(11d) R^1=OMe, R^2=H, X=NNHPh



(12a) X=O, R^1=H, R^2=OMe
(12b) X=NNHPh, R^1=H, R^2=OMe
(12c) X=NNHPh, R^1=OMe, R^2=H



(13a) R^1=H
R^2=OMe
(13b) R^1=OMe

these diulose derivatives, the crude oxidation-products which showed three main spots on tlc were separated by a silicagel column chromatography to give the 3-monouloses (11a[13,15] and 11b) [11b; mp 195-198°C, $[\alpha]_D$ -52° (c 0.7, acetone)] in 20% and 15% yields, respectively, which were further characterized as the phenylhydrazones (11c[15] and 11d) [11d; mp 173-175°C, $[\alpha]_D$ + 5° (c 0.4, $CHCl_3$), NMR(δ): 4.57 (H_4; d, $J_{4,5}$= 9.0), 4.30 (H_1 ; d, $J_{1,2}$= 7.0). 3.77 (H_2; d)]. Condensation of pure 11a and 11b with 1,2-diaminobenzene gave quantitatively 13a and 13b respectively, but only 11c and 11d, instead of 12b and 12c, could be obtained in the reaction with phenylhydrazine under various conditions. The former result indicates that the Amadori-type rearrangement occurs in the intermediary step, and that the formation of 13a and 13b does not always imply the presence of 2,3-diuloses in the reaction mixture. While, the latter fact does not exclude the presence of 2,3-diuloses in the crude oxidation-products, because a similar failure of the formation of 12b from 11c was also reported.[16]

Therefore, factors to control the reproducible formation of 12b and 12c in our experiments will remain ambiguous.

Analytical values of all compounds described here were satisfactory.

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