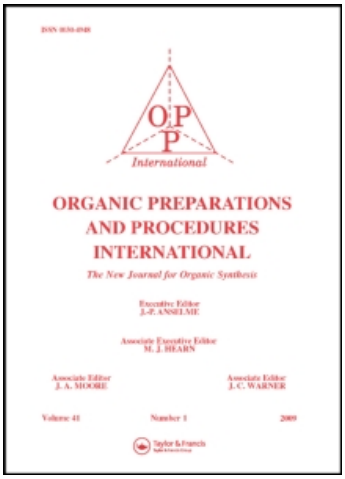

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CONVENIENT C-3 OXIDATION OF DEOXY AND AMINODEOXY SUGARS

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CONVENIENT C-3 OXIDATION OF DEOXY AND AMINODEOXY SUGARS†

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In spite of numerous reports,[1,3] the simple and efficient oxidation of primary or secondary hydroxyl groups of protected sugar derivatives to chiral synthons offering versatile possibilities for further transformations, is still a chaleng-ing synthetic problem. Arrick and coworkers[2] successfully oxidized the primary or exocyclic secondary hydroxyl groups of various carbohydrate derivatives with the chromium trioxide-pyridine complex.However the influence of the steric orienta-tion of the hydroxyl function to be oxidized (axial or equa-torial in hexopyranosides and exo or endo in five membered rings) on the yield was recognized, together with the formati-on of varying quantities of by-products. In addition, a fail-ure in analogous oxidations of isolated endocyclic hydroxyl groups attached to the ring-carbons of furanoid and pyranoid systems has been reported[2]. In contrast, Garegg and Samuelsson[3] showed that the addition of acetic anhydride as promoter to the in situ generated chromium trioxide-pyridine complex in dichloromethane resulted in the rapid oxidation (10-15 min) of primary or secondary alcohol functions of carbohydrates to

carbonyl groups, even in cases when other oxidation methods failed. Our study of the syntheses and transformations of deoxy and aminodeoxy sugars led us to extend the Garegg--Samuelsson procedure[3] to protected 2-deoxy- and 2-amino-2-deoxy sugar derivatives. The C-3 ulose compounds produced have turned out to be invaluable chiral synthons[4] for various synthetic conversions, including inversion of the configuration at C-3 and generation of axially- or equatorially-oriented amino functions; thus offers a simple access to 3-amino-2,3-dideoxy- and 2,3-diamino-2,3-dideoxyhexoses, as well as to C-3-branched carbohydrate derivatives etc.[5]

The starting materials, methyl 4,6-O-benzylidene-2-deoxy-β-D-arabino-hexopyranoside (1a)[6] and the corresponding α-D-ribo-analogue (1b)[7], methyl 2-benzamido-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside (1c)[8] and its 2-benzyloxycarbonyl derivative (1d)[9], methyl 2-benzamido-4,6-O-benzylidene-2-deoxy-α-D-allopyranoside (1e)[8] and methyl 2-benzamido-4,6-O-benzylidene-2-deoxy-α-D-altropyranoside (1f)[10] were prepared according to literature methods. Oxidation of compounds 1a-f was accomplished with a 1:4 molar ratio of the hydroxyl compound and the chromium trioxide-pyridine-acetic anhydride system in dry dichloromethane as detailed in Table 1 and in the general procedure. Under these conditions, no modification of the protecting groups was observed.

The ^{1}H-NMR data of the hexopyranosid-3-uloses obtained (1a-f) are summarized in Table 3.

The formation of by-products (such as the corresponding 3-O-acetate) was not observed in either of the oxidations. The high yields (88-98 %) of the ulose derivatives 2a-d clearly

prove that the oxidizing system used is not sensitive to steric factors and that it is useful for C-3 equatorial (1a,c, d) and axial (1b,e,f) hydroxyl compounds, irrespective of the size [bulky (1c-e) or small (1a,b)] of the equatorial substituent at C-2.

TABLE 1. Conversion of 1a-f to Hexopyranosid-3-uloses (2a-d)

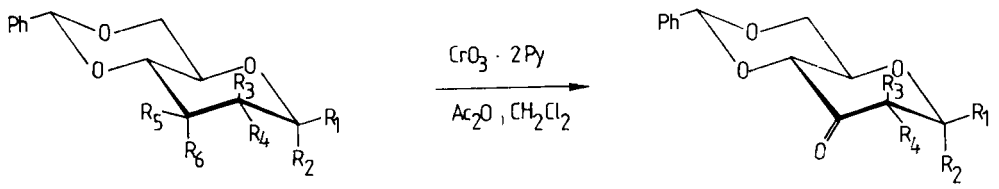
Starting material	Product	Time(min)	Yield(%)
1a	2a	80	88
1b	2b	80	97
1c	2c	35	98
1d	2d	45	96
1e	2c	35	96
1f	2c	40	94

TABLE 2. Physical Data for C-3 Uloses (2a-d)

Cmpd	mp. (°C)	$[\alpha]_D^{23}$ ($CHCl_3$)	Elemental Analyses Calcd (Found)				TLC
			C	H	N		
2a	201-202	-43.0	63.62(63.37)	6.11(6.39)	-	-	A
2b	170-171	+133.8	63.62(63.51)	6.11(5.84)	-	-	B
2c	212(dec.)	+138.0	65.62(65.56)	5.51(5.48)	3.64(3.58)		C
2d	208-209(dec.)	+88.5	63.91(63.80)	5.61(5.56)	3.39(3.42)		C

The rate of oxidation is independent of the anomeric configuration, while substitution with an electron-withdrawing moiety

at C-2 (i.e. in compounds 1c-e) seems to shorten the reaction time considerably.



1 2

	R_1	R_2	R_3	R_4	R_5	R_6
1a	OMe	H	H	H	OH	H
1b	H	OMe	H	H	H	OH
1c	H	OMe	H	NHBz	OH	H
1d	H	OMe	H	NHCbz	OH	H
1e	H	OMe	H	NHBz	H	OH
1f	H	OMe	NHBz	H	H	OH

	R_1	R_2	R_3	R_4
2a	OMe	H	H	H
2b	H	OMe	H	H
2c	H	OMe	H	NHBz
2d	H	OMe	H	NHCbz

Bz : COC_6H_5
Cbz: $COOCH_2C_6H_5$

In the case of the altropyranoside 1f, the oxidation proceeded with the inversion of the configuration of the axial benzamido group at C-2, to give 2c with physical data identical with those of the product obtained from 1c and 1e. Similar results have been reported by Baker and Buss[8] and Ali and Richardson[11] in the oxidation of the corresponding C-2 acetamido or azido derivative, respectively, by the Pfitzner-Moffat reagent or with dimethylsulfoxide-acetic anhydride. It is most probable that the inversion of the axial C-2 benzamido group, close to the site of oxidation, proceeds via an acid-catalyzed enolization involving a carbanion at C-2.

TABLE 3. ^{1}H-NMR(δ) and Coupling Constans (Hz) of C-3 Ketosugars

Hydrogen	2a	2b	2c	2d
ArH	7.30-7.60	7.30-7.60	7.30-7.95	7.38-7.53
H_1	4.78	5.15	5.37	5.22
H_2	3.39	2.85	-	-
$H_{2'}$	3.23	2.67	5.15	4.65
H_4	4.34	4.32	4.48	4.48
H_5	3.67	4.17	4.15	4.15
H_6	4.48	4.41	4.43	4.38
$H_{6'}$	3.92	3.92	4.03	3.95
NH	-	-	6.95	5.63
$J_{1,2}$	3.0	4.0	-	-
$J_{1,2'}$	8.0	1.0	4.4	4.5
$J_{2,2'}$	14.5	14.5	-	-
$J_{4,5}$	9.5	10.5	9.5	9.5
$J_{5,6}$	5.0	4.5	4.0	4.1
$J_{5,6'}$	10.0	10.0	9.9	9.8
$J_{6,6'}$	10.5	10.0	9.9	9.8
$J_{2,NH}$	-	-	8.0	6.0

EXPERIMENTAL SECTION

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Specific optical rotations were measured with a Perkin-Elmer Polarimeter 241. The ^{1}H-NMR spectra (200 MHz) were recorded with a Bruker WP 200 SY instrument for solutions in $CDCl_3$ (TMS internal standard). Dichloromethane was distilled from P_2O_5 and kept over 3 Å molecular sieves. Pyridine was purified by distillation from P_2O_5 and stored over KOH. Chromium trioxide (Fluka p.a.) was dried over P_2O_5 in a vacuum desiccator. Ethyl acetate was freed from acid and alcohol. Thin layer chromatography was performed on precoated silica gel plates (Merck 60 F_{254}) with the solvent systems: (A) chloroform; (B) 98:2 chloroform-methanol and (C) 7:3 chloroform-acetone. For column chromatography, Kieselgel 40 (Merck) was used.

General Procedure for Oxidation. For 10 mmol of the sugars

(1a-f) to be oxidized the chromium trioxide-pyridine complex was prepared by the addition of dry chromium trioxide (4.0 g; 40 mmol) to a mixture of dry dichloromethane (85 ml) and dry pyridine (6.44 ml, 80 mmol) with vigorous stirring. The mixture was stirred at room temperature for 15 min and a concentrated solution of 1a or 1b or a dilute suspension of 1c-f in dry dichloromethane, and acetic anhydride (3.80 ml; 40 mmol) were added to the deep-red solution. A tarry deposit formed almost at once and the color of the solution changed to dark-brown. The reaction was monitored by TLC and when all the starting sugar had reacted, the mixture was poured onto the top of a short column filled with silica gel and ethyl acetate, and the product was separated from the precipitated chromium compounds by means of adsorptive filtration with ethyl acetate as the eluent. The colorless eluate was concentrated under diminished pressure at 40° (bath temperature) and the residue was co-distillated with toluene to remove traces of acetic acid and pyridine. The products were recrystallized from methanol. The physical data of the hexopyranosid-3-uloses obtained (2a-d) are summarized in Table 2.

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