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A Novel General Method for 2-Aminoglycal Synthesis

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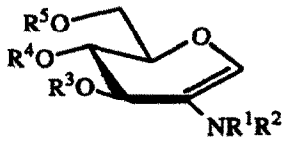
Abstract: The first general method for *N,N*-substituted 2-aminoglycals is reported. We describe the syntheses of 2-[(*N*-acyl-*N*-alkyl)amino] and 2-[(*N,N*-dialkyl)amino]-1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-*erythro*-hex-1-en-3-uloses by oxidation of glycoside derivatives of *N,N*-substituted-2-aminosugars using two oxidant systems. Reactions proceed with good yields.

Glycal derivatives have played a major role in carbohydrate chemistry as precursor substances in the synthesis of glycosides[1], thioglycosides[2], oligosaccharides[3], 2-deoxynucleosides[4] and C-glycosides[5], as well as in that of α, β-unsaturated lactones[6].

There are many works on glycal and 2-hydroxyglycal[7] preparation, but many fewer on the synthesis of hex-1-en-3-ulose derivatives[8]. Moreover there are scarce antecedents for the preparation of 2-aminoglycal derivatives (**1**) and (**2**).



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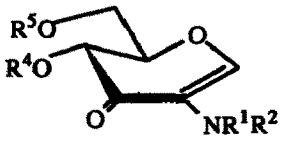
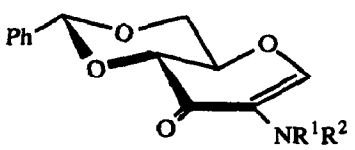


2

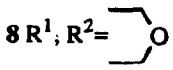
Such antecedents for the preparation of compounds **1** and **2** refer to non-general procedures of certain substances with acetyl or methyl group on the nitrogen[9], or of other substances obtained as unwanted byproducts in glycosidation[10] or α-methylation of ketones[11].

In view of the scarcity of the antecedents found and due to our interest in 2-aminoglycal derivatives, in this paper we describe for the first time a good general method for the synthesis of 2-[(*N*-acyl-*N*-alkyl)amino]-1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-*erythro*-hex-1-en-3-uloses.

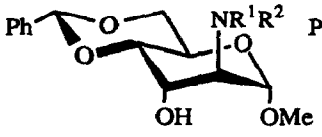
This general method consists of the oxidation of glycoside derivatives of *N,N*-substituted-2-aminosugars. Here, we describe the synthesis of substances **3-8** from 2-aminosugars (**9-19**)[12] using two

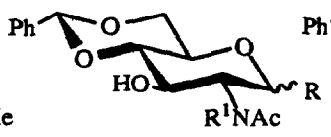


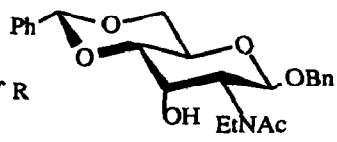
3 R^1=Bn; R^2=BOC
4 R^1=Bn; R^2=Ac
5 R^1=$nC_{12}H_{25}$; R^2=Ac
6 R^1=Me; R^2=Ac
7 R^1=Et; R^2=Ac

8 R^1, R^2= 

oxidant systems: PCC/CH_2Cl_2 and DMSO/DCC. A typical procedure for each reaction is given below.







9 R^1=Bn; R^2=BOC
10 R^1=Bn; R^2=Ac
11 R^1=$nC_{12}H_{25}$; R^2=Ac

12 R^1, R^2= 

13 R= αOBn; R^1=Bn
14 R=βOBn; R^1=Bn
15 R=αOBn; R^1=Me
16 R=αOBn; R^1=Et
17 R=βOBn; R^1=Et
18 R=β$OnC_{12}H_{25}$; R^1=Et

19

The results of the oxidation reaction for the different compounds studied are recorded in Table 1. Analysis of the results reveals the general character of the procedure. It is noteworthy that the reactions give good yields using the two procedures, and byproducts are not detected. In addition, it is important to point out the ready preparation of 2-aminoglycal derivatives independently of the nature of the aglycon and nitrogen substituents and the configuration on the carbons C1, C2 and C3 of the starting aminosugar.

Table 1. 2-Aminoglycal derivatives by oxidation of *N,N*-substituted-2-aminoglycosides.

Entry	Starting material	Procedure	Product	Yield (%)[a]	MS(CI) $[M+H]^+$ (% intensity)	
1	**9**	A	**3**	80	438	(<5)
2	**10**	A	**4**	84	380	(100)
3	**10**	B	**4**	90	380	(100)
4	**11**	A	**5**	87	458	(100)
5	**11**	B	**5**	78	458	(100)
6	**12**	B	**8**	72	318	(100)
7	**13 or 14**	A	**4**	80-84	380	(100)
8	**13 or 14**	B	**4**	88-91	380	(100)
9	**15**	B	**6**	86	304	(100)
10	**16 or 17**	B	**7**	75-77	318	(100)
11	**18**	B	**7**	80	318	(100)
12	**19**	B	**7**	76	318	(100)

[a]The yield refers to the isolated yield.

These results contrast with those obtained in the oxidation of glycoside derivatives from glucose and altrose. Thus, when we oxidized (using the same procedures) methyl 4,6-*O*-benzylidene-2-*O*-pivaloyl-α-D-gluco- (or altro) pyranoside, the 3-ulose derivatives were obtained, with good yield, without 2-*O*-pivaloylglycal formation.

The products obtained were characterized by their elemental analyses, MS (EI and CI) and NMR data[13].

Currently we are studying the reactivity of the obtained products with different nucleofiles.

Procedure A:

To a solution of 2-(*N*-acyl-*N*-alkyl)-aminosugar (2.0 mmol) in dry dichloromethane (40 mL) was added pyridinium chlorochromate (4 mmol) and 3 Å molecular sieves (10 g). The reaction mixture was well stirred overnight at room temperature. After completion of reaction (tlc), diethylether was added and filtered through a glass filter filled with silica gel containing $CaSO_4$ (10 %). Removal of the solvent by evaporation *in vacuo* gave a pure compound.

Procedure B:

To a stirred mixture of 2-(*N*-acyl-*N*-alkyl) or 2-(*N,N*-dialkyl)-aminosugar (2.0 mmol), 3 Å molecular sieves (1 g) and anhydrous dimethyl sulphoxide (30-40 mL), cooled to 0°, dicyclohexylcarbodiimide (8.0 mmol) was added. After ten minutes, anhydrous orthophosphoric acid (8.4 mmol) was then added portion-wise with cooling (ice bath) so that the temperature was kept at 25-30°. The reaction mixture was stirred for 24 hours at room temperature. The solids were removed by filtration and washed with dimethyl sulphoxide and acetone. The solution was diluted with four volumes of dichloromethane, water was added, and then a potassium carbonate solution (2.4 M) was added to bring the aqueous phase to about pH 8. The aqueous layer was extracted with dichloromethane and the combined extracts were washed with water until neutral. The organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to dryness. The solid obtained was crystallized or fractionated by chromatography on a silica gel column.

Acknowledgements

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12. For the synthesis of new starting material (**9-19**), described methods are used[14]; such products will be described in a forthcoming paper.
13. For **4**: (Found: C, 69.43; H, 5.76; N, 3.74; $C_{22}H_{21}NO_5$ requires C, 69.65; H, 5.58; N, 3.69). δ_H (500 MHz, DMSO-d_6, 25°) 7.62(s), 7.59(s) (1H, H-1), 4.94(d), 4.77(d) (1H, H-4), 4.68(m) (1H, H-5), 4.41(m) (1H, H-6_{eq}), 4.06(m) (1H, H-6_{ax}), 5.71(s), 5.69(s) (1H, PhC<u>H</u>), 5.08(dd), 3.96(dd) (2H, PhC<u>H</u>$_2$N), 1.98(s), 1.85(s) (3H, CH_3). δ_C (50Mz, DMSO-d_6, 25°)162.3, 161.9 (C-1), 120.5, 120.1 (C-2), 185.1, 184.8 (C-3), 75.1 (C-4), 71.9 (C-5), 65.9 (C-6), 100.0, 99.8 (Ph<u>C</u>H), 50.4, 48.6 (Ph<u>C</u>H$_2$N), 170.4, 169.9 (CON), 20.9, 20.7 (CH_3). The assignment was confirmed by DEPT, COSY and CHCORR experiments. When we recorded the spectrum at 110° all double signals collapsed to single signals.
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