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3-DEOXYGENATION OF METHYL α-D-GLUCOPYRANOSIDES BY TREATMENT OF THEIR 3-O-(N,N-DIMETHYLSULFAMOYL) DERIVATIVES WITH SODIUM METAL IN LIQUID AMMONIA

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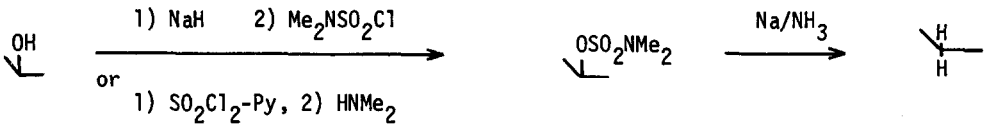
The selective deoxygenation of sugars and its application to aminoglycoside antibiotics[1] are of current interest, since the deoxygenated derivatives, such as 3'-deoxykanamycin A[2] and 3',4'-dideoxykanamycin B (dibekacin),[3] have been found to have remarkable activities against resistant bacteria. In α-D-glucopyranosides, however, the major difficulty lies in the deoxygenation of secondary hydroxyl groups attached to carbon atoms at which S_N2 processes are hindered. As an approach to this problem, radical-type deoxygenations have recently been developed,[4-11] and succesfully applied to the positions unsusceptible to the S_N2 reactions. In this paper, we report a new radical-type 3-deoxygenation of a number of methyl α-D-glucopyranoside derivatives, which involves treatment of their 3-O-(N,N-dimethylsulfamoyl) derivatives with sodium metal in liquid ammonia.

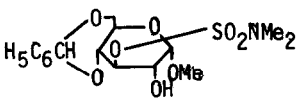
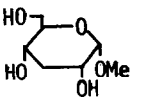
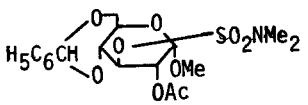
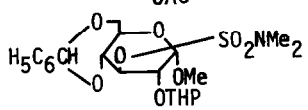
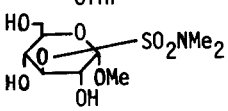
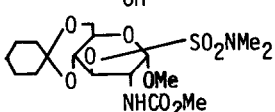
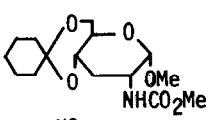
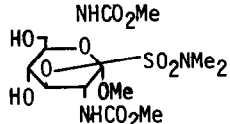
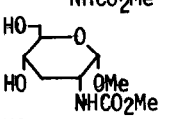
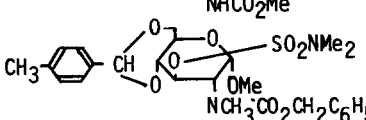
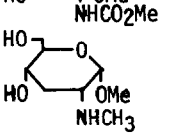
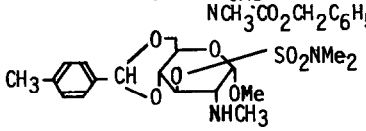
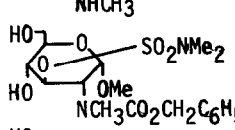
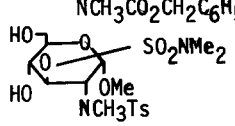
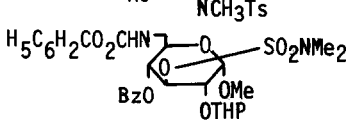
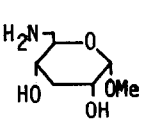
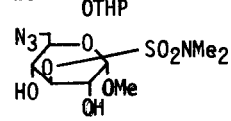
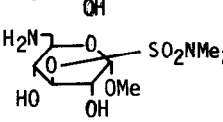
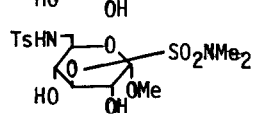
The starting N,N-dimethylsulfamoyl derivatives were prepared from the corresponding 3-hydroxyl compounds by reaction with sodium hydride and N,N-dimethylsulfamoyl chloride or with sulfuryl chloride, pyridine and dimethylamine. The latter reagent was useful even if the former reacts with difficulty and also useful when a strongly basic condition should be avoided. The 3-O-(N,N-dimethylsulfamoyl) derivatives were then dissolved in liquid ammonia or in liquid ammonia-THF (1:<0.25; useful when the derivative is not sufficiently soluble in liquid ammonia) and the solution was treated with sodium metal at -40 ~ -50°C. The corresponding 3-deoxy derivatives were prepared in high yields. The results are shown in Table 1.



The typical procedure is illustrated by the preparation of 7 as follows: To a cold (-5°C) solution of methyl 4,6-O-cyclohexylidene-2-deoxy-2-methoxycarbonylamino-α-D-glucopyranoside (2 g) in DMF (15 ml), 50% oily sodium hydride (220 mg as NaH) was added and after vigorous stirring (20 min), N,N-dimethylsulfamoyl chloride (1.32 g) was added and the stirring was continued for further 1 h at the temperature. The reaction mixture was poured into water and the precipitate was purified in a usual manner to give 6 (76% after recrystallization from n-hexane), $[\alpha]_D^{25}$ +47° (c 1, MeOH), δ($CDCl_3$): 2.94 (6H s, SO_2NMe_2), 3.41 (3H s, OMe), 3.75 (3H s, CO_2Me). The alternative reaction is as folloes: To a cold (-15°C) solution of the 3-hydroxyl compound (2.0 g) in CH_2Cl_2 (20 ml), pyridine (1.17 ml) and SO_2Cl_2 (980 mg) were added and the solution was kept at the temperature for 30 min to give a 3-O-chlorosulfonyl derivative (unstable), which was treated with $HNMe_2$ in CH_2Cl_2 at room temperature to give 6 (72%). To a solution of 6 (100 mg) in liquid ammonia (~8 ml, at -50°C), a piece of sodium metal was added and the deep-blue solution was kept for 1 h at the temperature. After addition of methanol (color disappeared) followed by evaporation of ammonia, the residue was dissolved in chloroform and processed in a usual manner to give methyl 4,6-O-cyclohexylidene-2,3-dideoxy-2-methoxycarbonylamino-α-D-glucopyranoside (7, 60 mg, 83%). Decyclohexylidenation (50% AcOH, 60°C) gave methyl 2,3-dideoxy-2-methoxycarbonylamino-α-D-glucopyranoside (9) identical with the product prepared from 8 by the reaction with Na-NH_3; $[\alpha]_D^{25}$ +126° (c 1, MeOH); δ(D_2O): 1.66 (1H q, J 12 Hz, H-3_{ax}), 2.13 (1H double t, J 4.5, 4.5 and 12 Hz). When the final product is water-soluble (products from 1, 3 ~ 5, 10 ~ 19), an aqueous solution of the product obtained after evaporation of ammonia was passed through a column of Dowex 50W resin (H^+ or NH_4^+ form), and the column was washed with water (in the cases of 1, 3 ~ 5) or with aqueous ammonia (~1 M, in the cases of 10 ~ 19) to give a 3-deoxy derivative free from sodium ion.

These results show that 3-deoxygenation were successfully performed on the derivatives of methyl α-D-glucopyranosides, and the protecting groups on the starting compounds do not interfere with this reaction although benzylidene, tolylidene, O-acetyl, N-benzyloxycarbonyl, N-tosyl , and azide groups are eliminated or reduced (in the case of azide) simultaneously. Further studies concerning the scope and limitations of this reaction are in progress.

Table 1.

Starting Material[a]		Product[b]		Yield
	(1)		(2)[c]	55 %
	(3)	" [d]		51 %
	(4)	" [d]		80 %
	(5)	"		69%
	(6)		(7)	83 %
	(8)		(9)	91%
	(10)		(11)[e]	84 %
	(12)	"		85 %
	(13)	"		82 %
	(14)	"		90 %
	(15)		(16)[d,f]	70 %
	(17)	"		81 %
	(18)	"		75 %
	(19)	"		79 %

[a] The detailed preparation of the starting materials will be reported in a full paper. [b] On checking by tlc, the reaction products obtained from 1, 3 and 5 gave the same two major spots, one of which being 2. Structural study of the by-product is now in progress. The reaction products from the other materials gave substantially a single spot on tlc, respectively. [c] Thick syrup, $[\alpha]_D^{25}$ +159° (c 1, MeOH); $\delta(D_2O)$: 1.70 (1H q, J 11 Hz, H-3_{ax}), 2.18 (1H double t, J 5, 5 and 11 Hz, H-3_{eq}), 3.50 (3H s, OMe), 4.76 (1H d, J 3 Hz, H-1). This compound did not reacted with aqueous sodium metaperiodate. [d] The acyl group was removed during purification and the THP group was also removed during Dowex 50W (H^+) resin treatment. [e] Thick syrup, $[\alpha]_D^{25}$ +138° (c 1, MeOH) (as free base); $\delta(D_2O)$: 1.45 (1H q, J 12 Hz, H-3_{ax}), 2.20 (1H double t, J 4.5, 4.5 and 12 Hz, H-3_{eq}), 2.74 (1H double t, J 3.5, 4.5 and 12 Hz, H-2), 2.37 (3H s, NMe), 3.48 (3H s, OMe), 4.81 (1H d, J 3.5 Hz, H-1). [f] Thick syrup, $[\alpha]_D^{25}$ +172° (c 1, MeOH) (as free base); $\delta(D_2O)$: 1.68 (1H d, J 11.5 Hz, H-3_{ax}), 2.22 (1H double t, J 5, 5 and 11.5 Hz), 3.54 (1H s, OMe), 4.80 (1H d, J 3 Hz, H-1).

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