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Synthesis of Some 1,6-Anhydro Disaccharides via Aryl Glycosyl Sulfones

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1,6-Anhydro-lactose, -maltose, and -cellobisoe were practically prepared in mild reaction conditions and in fairly good yield via alkaline degradation of various aryl glycosyl sulfones derived from the corresponding disaccharides.

1,6-Anhydro disaccharides are versatile intermediates for the chemical transformation[1-5] of common disaccharides, and the modified synthetic methods[1,2,6] as well as the conventional ones[7] have extensively been exploited so far.

However, most of these methods have still some intrinsic disadvantages in terms of the reaction conditions, the yield and so on, actually because they have mainly depended upon the alkaline degradation of phenyl or substituted phenyl glycosides. Even the modified procedure[6] requires a rather prolonged reaction time and a higher reaction temperature.

In order to overcome such drawbacks, it seems to be requisite for us to adopt a better leaving group such as alkyl- or aryl-sulfonyl group as an aglycone in place of the conventional phenoxy or halophenoxy group having potential limitations.[8]

The survey of the literatures gave us a suggestive paper[9] reported by Richtmyer et al, who had happened to describe the conversion of β-D-glucopyranosyl *p*-tolyl sulfone into 1,6-anhydro-β-D-glucopyranose(levoglucosan) in addition to the major subject about the oxidation-acetylation of *p*-tolyl 1-thio-β-D-glucopyranoside. However, no detailed informations concerning the yield and the optimal conditions were available in that paper.

Thus, we attempted to develop the above method by searching out the most suitable conditions for general synthesis of 1,6-anhydro disaccharides from various aryl glycosyl sulfones. Therefore, aryl 1-thio-β-D-glycosides[10] (1a, 1c, 1e, 1g, 2a, 2c, and 2e) of lactose, maltose, and cellobiose were prepared respectively either by the standard reaction[11] between the corresponding glycosyl bromides and sodium arylthiolates, or by the direct S-glycosidation[12] of the disaccharide peracetates with arylthiol in the presence of Lewis acids. Aryl 1-thio-glycosides thus obtained were then oxidized with excess amount of 30% hydrogen peroxide in acetic acid to the corresponding aryl glycosyl sulfones[13] (1b, 1d, 1f, 1h, 2b, 2d, and 2f) in yields 80-93%.

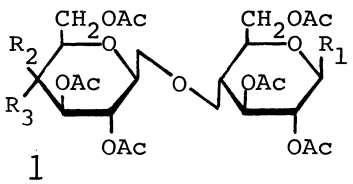
Those aryl glycosyl sulfones were then subjected to several alkaline conditions as is shown in the table. Although the best results are obtained in the

entry No.2 and No.9 (condition B) as far as the yield is concerned, the result of condition C is also satisfactory except entry No.11 judging from easy work-ups, and the comparison of the entry No.3 with No.5, No.8 with No.10, and No.13 with No. 14 demonstrates that 4-chlorophenylsulfonyl group is a better leaving group than phenylsulfonyl group. Such tendency, however, is not clearly observed in the condition B. Ethyl sulfonyl derivative (2f, entry No.11) is not suitable for this reaction, and the low yield is probably due to the increased side-reactions, which were also observed to a less extent in other cases.[14)]

Table 1. Reaction of aryl glycosyl sulfones in several alkaline conditions

Entry	Substrates	Conditions	Products[d)]	Yield /%
1	1b	A[a)]	3a	75
2	1b	B[b)]	3a	87
3	1b	C[c)]	3a	74
4	1d	B	3a	77
5	1d	C	3a	76
6	2b	A	4	64
7	2b	B	4	81
8	2b	C	4	70
9	2d	B	4	83
10	2d	C	4	75
11	2f	C	4	29
12	1f	B	3b	75[e)]
13	1f	C	3b	70[e)]
14	1f	C	3b	79[e)]

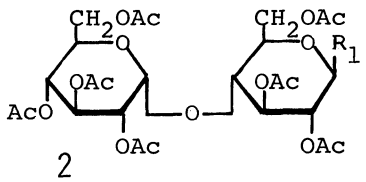
a) Refluxed with 2 mol KOH for 3 h. b) Deacetylated with CH_3ONa/CH_3OH at room temperature, and concentrated in vacuo to a residue, which was treated with 2 mol KOH as above. c) Refluxed with CH_3ONa(10 equiv.)/CH_3OH for 2 h.
d) All products were isolated as acetates. e) After column chromatography.



1

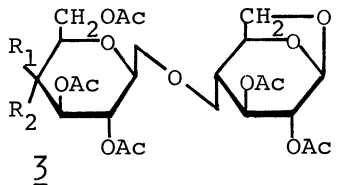
a: R_1= SC_6H_5
b: R_1= $SO_2C_6H_5$
c: R_1= $SC_6H_4Cl(p)$
d: R_1= $SO_2C_6H_4Cl(p)$
(R_2= OAc, R_3= H)

e: R_1= SC_6H_5
f: R_1= $SO_2C_6H_5$
g: R_1= $SC_6H_4Cl(p)$
h: R_1= $SO_2C_6H_4Cl(p)$
(R_2= H, R_3= OAc)



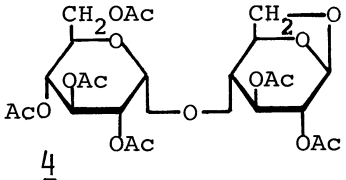
2

a: R_1= SC_6H_5
b: R_1= $SO_2C_6H_5$
c: R_1= $SC_6H_4Cl(p)$
d: R_1= $SO_2C_6H_4Cl(p)$
e: R_1= SC_2H_5
f: R_1= $SO_2C_2H_5$



3

a: R_1= OAc, R_2= H
b: R_1= H , R_2= OAc



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The typical procedures corresponding to the conditions B and C are briefly described respectively in the following.

(B) : Phenyl lactosyl sulfone heptaacetate (1a, 1 g) was treated with methanolic sodium methoxide (0.26 mol, 10 ml) at room temperature for 30 min, and concentrated *in vacuo* to dryness. The residue was then heated to reflux in aqueous potassium hydroxide (2 mol, 30 ml) for 3 h. The cooled reaction solution was neutralized with acetic acid, and concentrated again to a completely dried residue, which was conventionally acetylated with acetic anhydride (15 ml)/sodium acetate (1.5 g). After the usual work-up, the crystalline residue was recrystallized from ethanol to yield 2,3,2',3',4',6'-hexa-O-acetyl-1,6-anhydro-β-lactose (3a, 0.65 g, 87%), mp 209-210 °C, $[\alpha]_D^{25}$ -39.4° (c 1.0, $CHCl_3$); lit.[15] mp 206-208 °C, $[\alpha]_D^{17}$ -40° (c 1.0, $CHCl_3$).

(C) : Phenyl maltosyl sulfone heptaacetate (2b, 1 g) was heated to reflux in methanolic sodium methoxide (Na 0.3 g in methanol 30 ml) for 2 h, and concentrated *in vacuo* to a dry residue, which was then acetylated as above. Recrystallization of the crude acetate from methanol gave 2,3,2',3',4',6'-hexa-O-acetyl-1,6-anhydro-β-maltose (4, 0.53 g, 70%), mp 186-187 °C, $[\alpha]_D^{25}$ +49° (c 1.0, $CHCl_3$); lit.[1] mp 186-187 °C, $[\alpha]_D^{14}$ +49° (c 0.86, $CHCl_3$).

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8) The reported yield of aryl glycosides from the corresponding disaccharides is generally low ; I. C. M. Dea, Carbohydr. Res., 11, 363 (1969), ibid., 12, 297 (1970).
9) A. L. Clingman and N. K. Richtmyer, J. Org. Chem., 29, 1782 (1964).
10) Phenyl 2,3,6,2',3',4',6'-hepta-O-acetyl-1-thio-β-lactoside[11a,c] (1a), -β-cellobioside[11b,c] (1e), -β-maltoside[11b,c] (2a), the corresponding 4-chlorophenyl

1-thio-β-lactoside[11c] (1c) and -β-cellobioside[11d] (1g) were prepared respectively in a yield of 70-85% by the standard reaction, and the physical data of these compounds agreed well with the reported ones. Ethyl 2,3,6,2',3',4',6'-hepta-O-acetyl-1-thio-β-maltoside[12a] (2e) was prepared directly from maltose octaacetate in a yield of 81%.

4-Chlorophenyl 2,3,6,2',3',4',6'-hepta-O-acetyl-1-thio-β-maltoside (2c) was newly prepared in a yield of 72% by the direct reaction of maltose octaacetate with 4-chloro-thiophenol in the presence of $SnCl_4$;[12b] mp 143-144 °C, $[\alpha]_D^{25}$+39° (c 1.2, $CHCl_3$). The compounds (1e and 2a) were also prepared in a yield of around 70% by the above method, which was not always suitable for the preparation of lactose derivatives, because of the low solubility of lactose octaacetate in benzene.

11) a) E. Fischer and K. Delbrück, Ber., 42, 1476 (1909); b) C. B. Purves, J. Am. Chem. Soc., 51, 3619, 3631 (1929); c) G. Wagner and R. Metzner, Pharmazie, 24, 245 (1969); d) P. L. Durette and T. Y. Shen, Carbohydr. Res., 67, 484 (1978).

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13) A typical example is as follows : To a solution of phenyl 2,3,6,2',3',4',6'-hepta-O-acetyl-1-thio-β-cellobioside (1e, 7.3 g) in acetic acid (80 ml), was added 30% hydrogen peroxide (25 ml). The reaction solution was kept overnight at room temperature, and then poured into an ice-water (500 ml) with vigorous stirring. The precipitate was filtered, and the filtrate was extracted with chloroform. The precipitate and the extracted residue were recrystallized from ethanol to give the sulfone (1f), 6.0 g (82%); mp 219-220 °C, $[\alpha]_D^{25}$ -26° (c 1.0, $CHCl_3$); lit.[11c] mp 187-189 °C, $[\alpha]_D^{20}$ -23.9° (c 5.0, $CHCl_3$); PMR, IR, and elemental analysis support this structure. The physical data of other sulfones (1b, 1d, and 2b) agreed well with the reported ones.[11c]

The new sulfones (1h, 2d, and 2f) were isolated respectively in yields of 88%, 85%, and 93% ; 1h , mp 194-195 °C, $[\alpha]_D^{25}$ -35.4° (c 1.0, $CHCl_3$) ; 2d , mp 153-153 °C, $[\alpha]_D^{25}$ +41.3° (c 1.1, $CHCl_3$) ; 2f , amorphous powder, $[\alpha]_D^{26}$ +49.5° (c 1.5, $CHCl_3$).

14) One of by-products was isolated in the case of 1h (condition C) and tentatively assigned to be 4-chlorophenyl 3,6,2',3',4',6'-hexa-O-acetyl-2-O-methyl-β-cellobiosyl sulfone from PMR data (δ 4.38 ; 1H, H_1, d, $J_{1,2}$= 7.9 Hz, δ 3.48 ; 3H, s, OCH_3). This compound could be produced via β-elimination of acetoxy group at C-2 followed by β-addition of methoxy group to unsaturated sulfone.

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