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The Fusion Synthesis of Aryl 1-Thioglycosides

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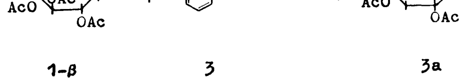
A simple method for the preparation of aryl 1-thioglycosides is described. The reaction of D-glucose pentaacetate or 2-acetamido-2-deoxy-D-glucose tetraacetate with arenethiols in the presence of zinc chloride under fusion conditions formed their 1-thioglycosides in good yields. Some Lewis acids in addition to zinc chloride were studied as catalysts in the reaction.

The Helferich method was applied successfully to the preparation of aryl 1-thioglycosides from sugar acetates with arenethiols.

The method is known as a simple and general procedure for the synthesis of aryl glycosides; it consists of fusing a sugar carboxylate and a phenol in the presence of an acid catalyst. The first extension of the method to the preparation of aryl 1-thioglycosides was attempted by Hurd and Bonner, who obtained phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-glucopyranoside (**3a**) from 1,2,3,4,6-penta-*O*-acetyl-*β*-D-glucopyranose (**1-*β***) and benzenethiol (**3**) with a *p*-toluenesulfonic acid or zinc chloride catalyst.[1] However, the yield of the product (**3a**) was very low. After that, in order to improve the yields, this acid-catalyzed condensation of sugar carboxylates with arenethiols has been performed on a solution using inert solvents; the method is considered to be a modification of the fusion synthesis.[2,3]

In the present work, we studied the condensation of D-glucose pentaacetate or 2-acetamido-2-deoxy-D-glucose tetraacetate with several arenethiols by the Helferich method, under fusion conditions and at much higher temperature than those shown in Hurd and Bonner's report,[1] and found that this simple procedure was superior to any other synthetic methods in the yields of products.

Thus, **1-*β*** was treated with **3** on fusion in the presence of zinc chloride to prepare a crystalline product which was identified with an authentic **3a**.[2] According to the GLC analysis of the reaction product, a small quantity of the 1-thio-*α*-glycoside (**3a-*α***) was contained in **3a**, but it was too small to isolate by a usual procedure using PLC silica-gel plates.[2] The reaction conditions, yield, and physical and analytical data of **3a** are shown in Table 1.



1-β 3 3a

1,2,3,4,6-Penta-*O*-acetyl-*α*-D-glucopyranose (**1-*α***) was also fused with **3** and a zinc chloride catalyst under similar conditions; the same product (**3a**) was thus obtained in a high yield, together with a small quantity of the 1-thio-*α*-glycoside (**3a-*α***), which was confirmed by comparing its physical data with those in the literature.[4]

Several arenethiols besides **3** were allowed to react with **1-*β*** and a zinc chloride catalyst under similar fusion conditions; *p*-chlorobenzenethiol (**4**), *o*-tolylthiol (**5**), *m*-tolylthiol (**6**), *p*-tolylthiol (**7**), *p*-*t*-butylbenzenethiol (**8**), and 2-naphthalenethiol (**9**).

The condensation products of **1-*β*** with **4**, **5**, **7**, and **9** were identified as *p*-chlorophenyl, *o*-tolyl, *p*-tolyl, and 2-naphthyl 2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-glucopyranoside (**4a**, **5a**, **7a**, and **9a**) respectively by comparing their physical data with those of the corresponding 1-thio-*β*-D-glucosides in the literature.[5—7] Also, the reaction products of **1-*β*** with **6** and **8** were confirmed to be *m*-tolyl and *p*-*t*-butylphenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-glucopyranoside (**6a** and **8a**) respectively on the basis of their physical and analytical data, which are summarized in Table 1.

1,3,4,6-Tetra-*O*-acetyl-2-acetamido-2-deoxy-*α*-D-glucopyranose (**2-*α***)[8] and its *β*-anomer (**2-*β***)[9,10] were also treated with **3** and the same catalyst on fusion to form an identical product, phenyl 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-1-thio-*β*-D-glucopyranoside (**3b**),[11] which was confirmed on the basis of its physical and analytical data, in good yields, but the 1-thio-*α*-glycoside was not found among those reaction products.

Similarly, the fusion reactions of **2-*α*** with the arenethiols, **4**, **5**, **6**, **7**, **8**, and **9**, gave their 1-thioglycosides, which were confirmed to be *p*-chlorophenyl, *o*-tolyl, *m*-tolyl, *p*-tolyl, *p*-*t*-butylphenyl, and 2-naphthyl 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-1-thio-*β*-D-glucopyranoside (**4b**, **5b**, **6b**, **7b**, **8b**, and **9b**) respectively on the basis of their physical and analytical data, as is summarized in Table 1.

Several Lewis acids in addition to zinc chloride were studied as catalysts in the reactions of **3** with **1-*α***, **1-*β***, **2-*α***, and **2-*β*** under definite conditions, as is shown in Table 2. Tin(II), tin(IV), and iron(III) chloride are effective as well as zinc chloride, although iron(III) chloride in the reaction with an *α*-acetate (**1-*α*** or **2-*α***) is a little inferior to the others. On the contrary, *p*-toluenesulfonic acid, phosphoryl chloride, and boron trifluoride, which are used often in the Helferich method, did not give good results in the present work.

In the Helferich reaction with simple phenols, the formation of *β*-glycosides was noted when *p*-toluenesulfonic acid, phosphoryl chloride, or tin(IV) chloride was utilized as the catalyst, whereas zinc chloride favored the formation of the *α*-anomers. However, the reaction with arenethiols is always favorable for the formation of 1-thio-*β*-glycosides, regardless of the catalyst.

TABLE 1. ARYL 1-THIOGLYCOSIDE ACETATES

Compound	Reaction[a] temp/°C (time/min)	Yield/%	Mp θ_m/°C (lit)	$[\alpha]_D^{20}$/° (in $CHCl_3$) (lit)	^1H NMR ($CDCl_3$):[b] δ (anomeric H) and J/Hz	Formula	Found (Calcd) (%)			
							C	H	S	N
3a	160 (50)	80	118 (117—118)[2]	−25.0 (−17.5)[2]	4.73 d, J=9.5	$C_{20}H_{24}O_9S$	54.72 (54.54)	5.35 (5.49)	7.41 (7.28)	
4a	170 (60)	83	113 (113)[5]	−25.7 (−25.0)[5]	4.72 d, J=9.5	$C_{20}H_{24}ClO_9S$	50.70 (50.47)	4.79 (5.08)	6.93 (6.74)	
5a	165 (55)	45	104—105 (104—106)[6]	−16.5 (−16.4)[6]	4.75 d, J=9.5	$C_{21}H_{26}O_9S$	55.65 (55.50)	5.64 (5.77)	7.19 (7.05)	
6a	165 (55)	58	93	−16.0	4.72 d, J=9.5	$C_{21}H_{26}O_9S$	55.73 (55.50)	5.51 (5.77)	6.98 (7.05)	
7a	165 (55)	64	118 (118)[5]	−21.5 (−21.0)[5]	4.68 d, J=9.5	$C_{21}H_{26}O_9S$	55.69 (55.50)	5.92 (5.77)	7.30 (7.05)	
8a	170 (60)	80	153	−22.5	4.73 d, J=9.7	$C_{24}H_{32}O_9S$	58.21 (58.05)	6.33 (6.50)	6.72 (6.46)	
9a	175 (50)	78	111 (111)[7]	−18.0 (−17.1)[7]	4.82 d, J=9.5	$C_{24}H_{26}O_9S$	58.89 (58.77)	5.30 (5.34)	6.76 (6.54)	
3b	175 (60)	66	200 (193—194)[11]	−39.1 (+10.5)[11]	4.94 d, J=9.8	$C_{20}H_{25}NO_8S$	54.92 (54.66)	5.81 (5.73)	7.13 (7.29)	3.30 (3.19)
4b	180 (55)	72	237	−29.8	4.78 d, J=9.5	$C_{20}H_{24}ClNO_8S$	50.92 (50.79)	5.32 (5.12)	6.88 (6.78)	3.15 (2.96)
5b	175 (60)	43	204	−21.2	4.83 d, J=9.5	$C_{21}H_{27}NO_8S$	55.48 (55.62)	6.20 (6.00)	6.82 (7.07)	3.22 (3.09)
6b	175 (60)	66	199	−20.5	4.92 d, J=9.5	$C_{21}H_{27}NO_8S$	55.41 (55.62)	6.18 (6.00)	6.91 (7.07)	3.10 (3.09)
7b	175 (60)	65	215—216	−21.5	4.83 d, J=9.5	$C_{21}H_{27}NO_8S$	55.69 (55.62)	6.23 (6.00)	6.89 (7.07)	3.31 (3.09)
8b	180 (60)	59	185	−20.3	4.94 d, J=9.8	$C_{24}H_{33}NO_8S$	58.31 (58.16)	6.58 (6.71)	6.40 (6.47)	2.73 (2.83)
9b	185 (55)	62	215	−10.6	4.94 d, J=9.8	$C_{24}H_{27}NO_8S$	59.01 (58.88)	5.44 (5.56)	6.68 (6.55)	2.77 (2.86)

a) A sugar acetate (**1-β** or **2-α**, 10 mmol), an arenethiol (13 mmol), and $ZnCl_2$ (*ca.* 0.05 g) were used. b) Other signals were commonly observed as follows: on **3a-9a**, δ=1.37 (9H, s, *t*-butyl), 2.00—2.10 (12H, 4×CH_3CO), 2.36 (3H, s, CH_3), 3.76—3.80 (1H, m, H-5), 4.20—4.30 (2H, oct, H-6,6′), 4.76—5.40 (3H, m, H-2, H-3, H-4), 7.00—8.00 (Aromatic H), on **3b-9b**, δ=1.37 (9H, s, *t*-butyl), 1.95—2.05 (12H, 4×CH_3CO), 3.70—3.80 (1H, m, H-5), 3.95—4.20 (3H, m, H-2, H-6,6′), 4.85—5.50 (2H, m, H-3, H-4), 5.85—6.60 (1H, d, NH), 7.00—8.00 (Aromatic H).

Table 2. Reaction of sugar acetates with benzenethiol in the presence of acid catalysts

Sugar acetate[a)]	Reaction temp/°C[b)]	Compound	Yield/%			
			$ZnCl_2$	$SnCl_2$	$SnCl_4$	$FeCl_3$
1-*α*	160	**3a**	73	67	50	37
		3a-*α*	4			
1-*β*	160	**3a**	80	75	52	61
2-*α*	175	**3b**	66	61	45	40
2-*β*	175	**3b**	68	59	47	52

a) A sugar acetate (10 mmol), benzenethiol (13 mmol), and an acid catalyst (*ca.* 0.05 g) were used. b) The reaction time was 60 min.

Experimental

All the melting points are uncorrected. The ^{1}H NMR spectra were measured with a JMN-4H-100 Spectrometer Japan Electron Optics Laboratory Co., Ltd.), using tetramethylsilane as the internal standard. The GLC analyses were performed with a JGC-20 KFP model (Japan Electron Optics Laboratory Co., Ltd.). A 2-m analytical column with 30% Silicone GE–SE 30 was used.

*Preparation of Aryl 1-Thioglycosides (**3a**, **4a**, **5a**, **6a**, **7a**, **8a**, **9a**, **3b**, **4b**, **5b**, **6b**, **7b**, **8b**, and **9b**) Listed in Table 1.* A mixture of a sugar acetate (**1-*β*** or **2-*α***; 10 mmol) and an arenethiol (**3**, **4**, **5**, **6**, **7**, **8**, or **9**; 13 mmol) was heated in an oil bath at the temperature shown in the second column in Table 1. After a few minutes, a catalytic amount of freshly fused and powdered zinc chloride (*ca.* 0.05 g) was stirred into the melt. The temperature of the oil bath was kept for the period given in Table 1. Then, the resulting colored melt was cooled and dissolved in ethanol (*ca.* 50 ml). After cooling in a freezer, the crystalline product was collected and recrystallized from ethanol. The yields and physical and analytical data of all the products are summarized in Table 1.

The melting point of **3a** was not depressed upon admixture with an authentic sample.[2)] The products, **4a**, **5a**, **7a**, and **9a**, were confirmed by comparing their melting points and specific rotation values with those in the literature.[5–7)] The other products, **6a**, **8a**, **3b**, **4b**, **5b**, **6b**, **7b**, **8b**, and **9b**, were confirmed on the basis of their analytical and NMR data, in which the signals of anomeric protons were observed at 4.68—4.94 ppm as a doublet, J=9.5—9.8 Hz, and on the basis of their specific rotation values, which were negative and not very different from each other.

Examination of Lewis Acids (Zinc Chloride, Tin(II) Chloride, Tin(IV) Chloride, and Iron(III) Chloride) in Table 2 as Catalysts. The Lewis acids were utilized as catalysts in the fusion reactions between **3** (13 mmol) and four sugar acetates (**1-*α***, **1-*β***, **2-*α***, and **2-*β***; 10 mmol). These reactions were performed under the definite conditions shown in Table 2, according to the procedure described above. Among them, the reaction of **1-*α*** with **3** in the presence of zinc chloride yielded a small amount of **3a-*α*** in addition to **3a** in the following manner. After the reaction mixture was fused, the resulting melt was dissolved in ethanol (*ca.* 50 ml), cooled, and filtered to obtain a crude crystalline product. It was recrystallized from ethanol to give **3a** (3.20 g, 73%). The mother liquor, which on GLC (the column was at 200 °C, and the carrier N_2 was 45 ml/min) showed two peaks, one appearing immediately after the other (corresponding to **3a**), was evaporated till *ca.* 20 ml under reduced pressure and then cooled. The colorless needles thus obtained were recrystallized from ethanol to yield **3a-*α*** (0.20 g, 4%), which, on GLC under the same conditions as above, showed just one peak; mp 90—91 °C, $[\alpha]_D^{20}$ +235° (c 0.52, $CHCl_3$), (lit,[4)] mp 91—92 °C, $[\alpha]_D^{20}$ +234° (c 1, $CHCl_3$)). ^{1}H NMR ($CDCl_3$), δ=2.00—2.12 (12H, 4×CH_3CO), 4.20 (2H, oct, H-6,6′), 4.60 (1H, m, H-5), 5.02—5.22 (2H, m, H-2, H-4), 5.50 (1H, t, H-3), 5.97 (1H, d, anomeric H, J=5.5 Hz), 7.25—7.60 (5H, aromatic H). Found: C, 54.72; H, 5.30; S, 7.40%. Calcd for $C_{20}H_{24}O_9S$: C, 54.54; H, 5.49; S, 7.28%.

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