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Synthesis of Glycosyl Trifluoroacetates and Their Reactions with Carboxylic Acids

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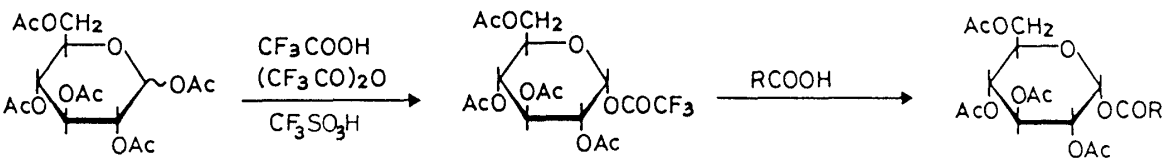
2,3,4,6-Tetra-*O*-acetyl-1-*O*-trifluoroacetyl-α-D-glucopyranose was prepared in a high yield by treating 1,2,3,4,6-penta-*O*-acetyl-α- or -β-D-glucopyranose with a mixture of trifluoroacetic acid and its anhydride in the presence of trifluoromethanesulfonic acid or antimony (V) fluoride-graphite catalyst. The reaction of the trifluoroacetate with some carboxylic acids afforded the corresponding 1-*O*-acyl-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoses. By a similar procedure, anomeric 1-*O*-trifluoroacetyl-2,3,5-tri-*O*-benzoyl- and -2,3,5-tri-*O*-acetyl-D-ribofuranose were obtained from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose respectively, and these trifluoroacetates were allowed to react with some carboxylic acids to yield the corresponding 1-*O*-acyl-β-D-ribofuranose benzoates and acetates. These products were also prepared by direct fusion of 1-*O*-acetyl-β-D-ribofuranose benzoate and acetate with the carboxylic acids.

Keywords——glycosyl trifluoroacetate; glycosyl carboxylate; fusion reaction; tetra-*O*-acetyl-α-D-glucopyranosyl trifluoroacetate; tri-*O*-benzoyl-α,β-D-ribofuranosyl trifluoroacetate; tri-*O*-acetyl-α,β-D-ribofuranosyl trifluoroacetate

There have been numerous attempts to prepare glycosyl carboxylates, a few of which have been found in nature, by using various reactions over the years. One method is based on the acid-catalyzed anomeric replacement reaction of aldose acetates with carboxylic acids.[1,2] The anomeric acetoxy group of an aldose acetate is more labile than the other acetoxy groups and is replaceable, when the acetate reacts with a carboxylic acid in the presence of an acid catalyst, by the corresponding acyloxy group.

Recently we converted 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose (1-α) and its β-anomer (1-β) into 2,3,4,6-tetra-*O*-acetyl-1-*O*-trifluoroacetyl-α-D-glucopyranose (**2**) by the acid-catalyzed replacement and found that the trifluoroacetoxy group of **2** was substituted much more readily than the anomeric acetoxy group of 1-α or 1-β, when **2** was treated with some carboxylic acids under mild conditions (even without any catalyst), by the corresponding acyloxy groups in α-D-configuration. These reactions were applied to the preparation of some D-ribofuranosyl carboxylates. The present work was carried out with the intention of preparing various D-glucopyranosyl and D-ribofuranosyl carboxylates through the trifluoroacetates.



1-α or 1-β 2

Chart 1

Thus, 1-α was treated with a mixture of trifluoroacetic acid and its anhydride containing a catalytic amount of trifluoromethanesulfonic acid to prepare a crystalline product in a high yield. By the same procedure, 1-β gave the same product in a similarly high yield. This was confirmed by comparing the physical and analytical data of the product with those reported by Studentsov *et al.* for **2** synthesized from 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose with trifluoroacetic anhydride.[3] In our reaction, antimony (V) fluoride-graphite (50%) was also an effective catalyst, as well as trifluoromethanesulfonic acid.

Then, **2** was allowed to react with several carboxylic acids, *i.e.*, trichloroacetic, chloroacetic, tribromoacetic, bromoacetic, cyanoacetic and benzoic acids (**3a**, **4a**, **5a**, **6a**, **7a** and **8a**), to yield the corresponding 1-*O*-acyl-α-D-glucopyranose acetates. In this preparative procedure, crude **2** was treated with each of these carboxylic acids at moderate temperatures under fusion conditions *in vacuo*, as summarized in Table I. The products from the reactions of **2** with **3a**, **4a**, **5a**, **6a** and **8a** were identified as 1-*O*-trichloroacetyl-, 1-*O*-chloroacetyl-, 1-*O*-tribromoacetyl-, 1-*O*-bromoacetyl- and 1-*O*-benzoyl-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (**3**,[1] **4**,[1] **5**,[4] **6**[4] and **8**[5]), respectively, by comparing their properties with those reported for the corresponding 1-*O*-acyl-α-D-glucopyranose acetates. The product formed from **2** and **7a** was confirmed to be 2,3,4,6-tetra-*O*-acetyl-1-*O*-cyanoacetyl-α-D-glucopyranose (**7**) on the basis of the physical and analytical data (summarized in Table I).

This replacement reaction at the anomeric center was applied to the preparation of some 1-*O*-acyl-D-ribofuranose benzoates and acetates. 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**10**) were converted into 2,3,5-tri-*O*-benzoyl-1-*O*-trifluoroacetyl-α,β-D-ribofuranose (**11**) and 2,3,5-tri-*O*-acetyl-1-*O*-trifluoroacetyl-α,β-D-ribofuranose (**12**), respectively, in good yields under conditions similar to those used for the trifluoroacetylation of 1-α or 1-β. These products were purified by silica gel column chromatography to give colorless syrupy materials, and were confirmed to be **11** and **12** on the basis of their physical and analytical data. They were anomeric mixtures as judged from their proton nuclear magnetic resonance (^{1}H-NMR) spectra. All attempts at chromatographic separation were unsuccessful.

The trifluoroacetates (**11** and **12**) were treated with the carboxylic acids, **3a**, **4a**, **5a**, **6a**, **7a** and **8a**, by the fusion procedure as described above. The reactions of **11** with **4a**, **6a**, **7a** and **8a**, and of **12** with **4a** and **6a** afforded crystalline products. However, the other reactions did not give good results. The products were confirmed to be 1-*O*-chloroacetyl-, 1-*O*-bromoacetyl- and 1-*O*-cyanoacetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**13**, **14** and **15**), 1,2,3,5-tetra-*O*-benzoyl-β-D-ribofuranose (**16**),[6] 1-*O*-chloroacetyl- and 1-*O*-bromoacetyl-2,3,5-tri-*O*-acetyl-β-D-ribofuranose (**17** and **18**), respectively, on the basis of the physical and analytical data, which are summarized, together with the conditions used, in Table II.

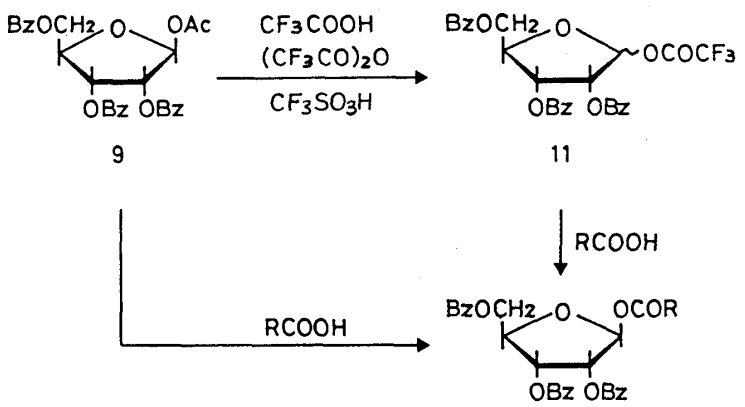


Chart 2

TABLE I. 1-*O*-Acyl-α-D-glucopyranose Acetates (**3**, **4**, **5**, **6**, **7** and **8**) Prepared from 1-*O*-Trifluoroacetyl-α-D-glucopyranose Acetate (**2**) with Carboxylic Acids (**3a**, **4a**, **5a**, **6a**, **7a** and **8a**)

Reactant	Conditions		Product	Yield (%)[b]	mp (°C) (lit.)	$[\alpha]_D^{22}$ (°)[c] (lit.)	^{1}H-NMR ($CDCl_3$): δ (anomeric H) and *J*/Hz	Formula	Analysis (%) Calcd (Found)		
	Temp. (°C)[a]	Time (min)							C	H	N
3a	45	30	**3**	45	127—128 (128)[1]	+99.2 (+98.1)[1]	6.43 d, *J*=3.2	$C_{16}H_{19}Cl_3O_{11}$	38.94 (39.13	3.85 3.82)	
4a	55	15	**4**	75	125 (125)[1]	+100.8 (+49.6)[1]	6.35 d, *J*=3.6	$C_{16}H_{21}ClO_{11}$	45.23 (45.15	4.95 4.92)	
5a	45	30	**5**	45	142—143 (137—139)[4]	+89.3 (+86.9)[4]	6.42 d, *J*=3.6	$C_{16}H_{19}Br_3O_{11}$	30.64 (30.78	3.03 3.17)	
6a	45	30	**6**	62	107—109 (98—100)[4]	+94.4 (+104.9)[4]	6.36 d, *J*=3.5	$C_{16}H_{21}BrO_{11}$	40.95 (40.79	4.48 4.33)	
7a	45	30	**7**	63	147—149	+101.2	6.38 d, *J*=3.3	$C_{17}H_{21}NO_{11}$	49.16 (49.29	5.06 5.30	3.37 3.30)
8a	45	30	**8**	44	106—108 (60—63)[5]	+125.6 (+113.5)[5]	6.57 d, *J*=3.8	$C_{21}H_{24}O_{11}$	55.75 (55.88	5.31 5.52)	

a) Temperature of water bath. *b*) Based on 1-β. *c*) (c=1.1, $CHCl_3$).

TABLE II. 1-*O*-Acyl-β-D-ribofuranose Benzoates (**13**, **14**, **15** and **16**) and Acetates (**17** and **18**) Prepared from 1-*O*-Trifluoroacetyl-α,β-D-ribofuranose Benzoate (**11**) and Acetate (**12**) with Carboxylic Acids (**4a**, **6a**, **7a** and **8a**)

Reactants	Conditions		Product	Yield (%)[b]	mp (°C) (lit.)	$[\alpha]_D^{22}$ (°)[c] (lit.)	^{1}H-NMR ($CDCl_3$): δ (anomeric H)	Formula	Analysis (%) Calcd (Found)		
	Temp. (°C)[a]	Time (min)							C	H	N
11 **4a**	50	30	**13**	53	183—184	+25.7	6.48 s	$C_{28}H_{23}ClO_9$	62.39 (62.44	4.27 4.35)	
11 **6a**	55	100	**14**	42	166—167	+22.6	6.45 s	$C_{28}H_{23}BrO_9$	57.64 (57.48	3.94 4.12)	
11 **7a**	50	30	**15**	25	189—193	+22.7	6.45 s	$C_{29}H_{23}NO_9$	65.78 (65.88	4.38 4.24	2.65 2.50)
11 **8a**	55	40	**16**	22	120 (120—121)[6]	+17.0 (+17.2)[6]	6.67 s	$C_{33}H_{24}O_9$	61.87 (62.01	5.87 5.98)	
12 **4a**	50	15	**17**	45	113.5—114.5	−23.1	6.21 s	$C_{13}H_{17}ClO_9$	44.27 (44.15	4.86 4.87)	
12 **6a**	50	15	**18**	40	95—97	−28.7	6.19 s	$C_{13}H_{17}BrO_9$	39.31 (39.44	4.31 4.35)	

a) Temperatures of water bath. *b*) Based on **9** or **10**. *c*) (c=1.0, $CHCl_3$).

TABLE III. 1-*O*-Acyl-β-D-ribofuranose Benzoates (**13**, **14** and **15**) and Acetates (**17** and **18**) Prepared from 1-*O*-Acetyl-β-D-ribofuranose Benzoate (**9**) and β-D-Ribofuranose Acetate (**10**) with Carboxylic Acids (**4a**, **6a** and **7a**)

Reactants		Catalyst[a]	Product	Conditions		Yield (%)
				Temp. (°C)[b]	Time (min)	
9	**4a**	None	**13**	150	30	40
		BF_3 etherate		130	2	75
		$ZnCl_2$		130	4	70
		ZnI_2		130	3	80
9	**6a**	None	**14**	150	20	38
		BF_3 etherate		130	2	48
		$ZnCl_2$		130	3	60
		ZnI_2		130	3	55
9	**7a**	None	**15**	150	20	32
		BF_3 etherate		130	2	65
		$ZnCl_2$		130	15	60
		ZnI_2		130	10	72
10	**4a**	None	**17**	150	20	65
		BF_3 etherate		95	15	46
		$ZnCl_2$		110	15	43
		ZnI_2		110	15	50
10	**6a**	None	**18**	150	20	58
		BF_3 etherate		100	10	42
		$ZnCl_2$		110	15	45
		ZnI_2		110	15	48

a) Reactions with zinc chloride and iodide were performed under reduced pressure (aspirator). *b*) Temperature of oil bath.

While several methods for preparing 1-*O*-acyl-α- and -β-D-glucopyranose derivatives, including the acid-catalyzed reaction of 1-α or 1-β with various carboxylic acids,[1,2] have been reported, the reaction of D-ribose derivatives has not yet been known. Therefore, preparation of 1-*O*-acyl-β-D-ribofuranose benzoates and acetates was performed by the fusion reactions of **9** and **10** with the carboxylic acids used in the above-mentioned reactions, in the absence or presence of an acid catalyst, such as boron trifluoride etherate, zinc chloride and iodide. The conditions used and the results are summarized in Table III. Among these carboxylic acids, **3a**, **5a** and **8a** did not give good results. The products were identical with those shown in Table II.

The preparation of 1-*O*-acyl-α-D-glucopyranose acetates (**3**, **4**, **5**, **6**, **7** and **8**) using the trifluoroacetate (**2**) was characterized by simple and easy procedures, and was not inferior to other synthetic methods in the yields of the products (since **2** was obtained in a high yield); further, all the products were of α-D-configuration.

Therefore, the D-ribofuranosyl carboxylate derivatives prepared by similar procedures were expected to have a clearly predominant configuration. However, **11** and **12** were mixtures of the anomers. The other products from the reactions of **9**, **10**, **11** and **12** with the carboxylic acids crystallized easily to give the β-anomers. They might contain small amounts of the α-anomers as noncrystalline materials in the reaction mixtures, although attempts at chromatographic isolation were unsuccessful.

Experimental

Melting points are uncorrected. Specific rotations were measured in a 1-dm cell with a DIP-4 digital polarimeter (Japan Spectroscopic Co., Ltd.). ^{1}H-NMR spectra were determined on a JMS-PS-100 spectrometer (Japan Electron

Optics Laboratory Co., Ltd.), using tetramethylsilane as the internal standard. Column chromatography was performed on silica-gel (Wakogel C-200, Wako Pure Chemical Ind., Ltd.) with benzene.

2,3,4,6-Tetra-*O*-acetyl-1-*O*-trefluoroacetyl-α-D-glucopyranose (2)——α-D-Glucopyranose pentaacetate (1-α) or its β-anomer (1-β) (3.9 g, 0.01 mol) was dissolved in a mixture of trifluoroacetic acid (25 ml), its anhydride (10 ml) and trifluoromethanesulfonic acid (0.5 ml), and the whole was stirred at room temperature for 2 h with exclusion of moisture. Then, the reaction mixture was evaporated to a syrup, which was further evaporated three times with the addition of 1,2-dichloroethane (*ca.* 30 ml each). The residual brownish syrup was treated wih cold 2-propanol (*ca.* 70 ml) to give white crystals, which were recrystallized from 2-propanol to yield **2** (3.9—4.1 g, 88—93%), mp 46—8 °C, $[\alpha]_D^{23}$ +85.3° ($c=1.1$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 6.48 (1H, d, anomeric proton, $J=3.3$ Hz). *Anal.* Calcd for $C_{16}H_{19}F_3O_{11}$: C, 43.25; H, 4.31; F, 12.83. Found: C, 43.42; H, 4.50; F, 13.12. [lit.[3] bp 118—120 °C (0.01 mmHg), $[\alpha]_D^{23}$ +93° ($c=0.3$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 6.48 ($J=4$ Hz). Found: F, 12.76].

When antimony (V) fluoride-graphite (50% (w/w)) (0.5 g) was used as a catalyst instead of trifluoromethanesulfonic acid, it was filtered off from the 1,2-dichloroethane solution, after the first evaporation as described above, and the yield of **2** was similar to that with trifluoromethanesulfonic acid.

2,3,5-Tri-*O*-benzoyl-1-*O*-trifluoroacetyl-α,β-D-ribofuranose (11)——Compound **9** (5.0 g, 0.01 mol) was treated with the same amount of the mixture for trifluoroacetylation [trifluroacetic acid, its anhydride and trifluoromethanesulfonic acid or antimony (V) fluoride-graphite (50% (w/w)) catalyst] in the same manner as described for the preparation of **2**. After evaporation of the 1,2-dichloroethane solution, the residual material was chromatographed on a silica gel column (2.6×18.0 cm) with benzene to yield a colorless syrup (4.3 g 78%), $[\alpha]_D^{21}$ +21.3° ($c=1.2$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 6.78 and 6.73 (1H, s each, anomeric proton; ratio of anomers, $\alpha/\beta=7/5$). *Anal.* Calcd for $C_{28}H_{21}F_3O_9$: C, 60.22; H, 3.79; F, 10.21. Found: C, 60.32; H, 3.70; F, 10.42.

2,3,5-Tri-*O*-acetyl-1-*O*-trifluoroacetyl-α,β-D-ribofuranose (12)——Compound **10** (3.2 g, 0.01 mol) was treated with the same amount of the mixture for trifluoroacetylation in the same manner as described for the preparation of **2**. Then, the product was purified by column chromatography on silica gel to give a colorless syrup (3.0 g, 81%), $[\alpha]_D^{22}$ +50.4° ($c=1.2$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 6.56 and 6.29 (1H, s each, anomeric proton; ratio of anomers, $\alpha/\beta=6/5$). *Anal.* Calcd for $C_{13}H_{15}F_3O_9$: C, 41.95; H, 4.06; F, 15.31. Found: C, 42.16; H, 4.21; F, 15.03.

1-*O*-Acyl-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (3, 4, 5, 6, 7 and 8) Listed in Table I——Carboxylic acids, **3a**, **4a**, **5a**, **6a**, **7a** and **8a** (0.025 mol each) were allowed to react with crude **2**, prepared from 1-α or 1-β (3.9 g, 0.01 mol) by the procedure described earlier without crystallization from 2-propanol. A mixture of **2** and one of these carboxylic acids was heated with stirring under reduced pressure, and then was treated with ethanol to obtain a crystalline product, which was recrystallized from the same solvent. The reaction conditions and the results are summarized with the physical and analytical data of all these products in Table I.

1-*O*-Acyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoses (13, 14, 15 and 16) and 1-*O*-Acyl-2,3,5-tri-*O*-acetyl-β-D-ribofuranoses (17 and 18) Listed in Table II——Carboxylic acids, **4a**, **6a**, **7a** and **8a** (0.025 mol each) were allowed to react with crude **11**, prepared from **9** (5.0 g, 0.01 mol) by the procedure described for the preparation of **11** without chromatographic purification. A mixture of **11** and one of these carboxylic acids was heated with stirring under reduced pressure, and then was treated with ethyl acetate. The crystalline product was recrystallized from the same solvent.

The reactions of crude **12**, obtained from **10** (3.2 g, 0.01 mol) by the procedure described for the preparation of **12** without chromatographic purification, with **4a** and **6a** (0.025 mol each) were carried out just as mentioned above. The products were crystallized and recrystallized from ethanol.

The reaction conditions and the results are summarized with the physical and analytical data of the products in Table II.

1-*O*-Acyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoses (13, 14 and 15) and 1-*O*-Acyl-2,3,5-tri-*O*-acetyl-β-D-ribofuranoses (17 and 18) Listed in Table III——Compound **9** (5.0 g, 0.01 mol) or **10** (3.2 g, 0.01 mol) was mixed with a carboxylic acid (**4a**, **6a** or **7a**, 0.025 mol each) and heated under the conditions shown in Table III. Noncatalytic reactions were carried out at atmospheric pressure to avoid evaporation of the carboxylic acids at the relatively high temperature. When boron trifluoride etherate (0.1 ml) was employed, the reactions were also performed at atmospheric pressure to avoid a decrease of the volatile catalyst. The other catalysts, zinc chloride and iodide (0.05 g each), were used under reduced pressure. The resulting melts were crystallized from ethanol (*ca.* 80 ml). The products, **13**, **14** and **15** were recrystallized from ethyl acetate, and **17** and **18** from ethanol.

The reaction conditions and the yields of all the products are summarized in Table III.

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