Temperature Dependence of the Distribution of Trityl Groups in the Tritylation of 1,2-*O*-Isopropylidene-α-D-glucofuranose

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The tritylation reaction of 1,2-*O*-isopropylidene-α-D-glucofuranose with 2.4 molar amounts of trityl chloride in pyridine at 70 °C for 20 h gave the 5,6-di-*O*-trityl derivative in 50% yield as the major product, whereas the reaction at 115 °C mainly gave the 3,6-di-*O*-trityl derivative (26% yield) along with the 6-*O*-trityl derivative (48% yield). The fact that the yield of the 5,6-di-*O*-trityl derivative at 115 °C decreased after 1 h and was 12% at 20 h is due to the redistribution of trityl groups including detritylation assisted by pyridinium chloride. It was found that tritylation of the primary hydroxyl group at C-6 was almost completed within 10 min at 115 °C.

Key words tritylation; temperature dependence; 1,2-*O*-isopropylidene-α-D-glucofuranose; redistribution; pyridinium chloride

The trityl group is well known as a protecting group of the primary hydroxyl group of carbohydrates.[1—6] However, tritylation of the secondary hydroxyl group has often occurred,[2,4—14] and was successfully used in the preparation of some partially benzylated monosaccharides.[14]

To prepare a series of nucleoside analogues which have modified hexofuranoses as the sugar moiety, we substituted the 5-hydroxyl group of hexofuranoses by a fluorine atom, a hydrogen atom, or an azido group with the 6-hydroxyl group remaining free. Simultaneous introduction of trityl groups to the 3- and 6-positions of 1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) would be most convenient to prepare a substrate of the substitution reactions at the 5-position.

Although the tritylation reaction with trityl chloride in pyridine of the primary hydroxyl group proceeded smoothly, that of the secondary hydroxyl group depends on its reactivity and steric requirement. The fact that the tritylation reaction of methyl α-D-mannopyranoside gave three di-*O*-trityl derivatives with different ratios depending on the reaction temperature is already known.[14] The time course of the product distribution suggested that the migration-like alternative detritylation–tritylation reactions occurred and that the detritylation reaction was caused by pyridinium chloride produced during the tritylation reaction.

In the present article, we report the results of the tritylation reactions of **1** with trityl chloride in pyridine.

Results and Discussion

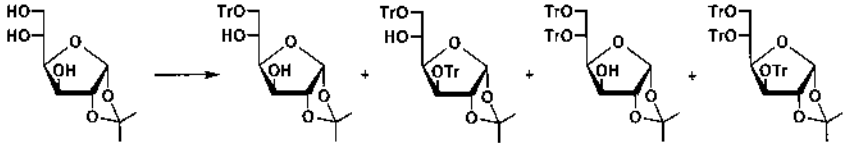
Compound **1** was reacted with 2.4 molar amounts of trityl chloride in pyridine at 70 °C for 20 h to give 1,2-*O*-isopropylidene-5,6-di-*O*-trityl-α-D-glucofuranose (**4**) in 50% yield as the major product. 1,2-*O*-Isopropylidene-3,6-di-*O*-trityl-α-D-glucofuranose (**3**) was isolated from the reaction mixture in only 10% yield, and the yield of 1,2-*O*-isopropylidene-6-*O*-trityl-α-D-glucofuranose[15,16] (**2**) was 36% (Table 1). The reaction at 50 °C gave **3** and **4**, each in almost half the yield of those at 70 °C. In both cases, almost no 1,2-*O*-isopropylidene-3,5,6-tri-*O*-trityl-α-D-glucofuranose (**5**) was produced. These facts indicate that the secondary hydroxyl group at C-5 (OH-5) is essentially more reactive with trityl chloride than the other one at C-3 (OH-3) even under a situation where the 6-*O*-trityl group has already existed.

The structure of these compounds was confirmed by H–H and C–H correlation spectroscopy (COSY) measurements in NMR spectroscopy. As supporting proof of the position where a hydroxyl group remains free in **3** and **4**, an acetylation shift of the signal of the proton at that position was obsreved.

Remarkable changes in distribution of the products were noted when the reactions were conducted at higher temperatures; the yields of **3** and **5** increased and that of **4** decreased at 95 °C, and this tendency became more obvious at 115 °C (Table 1). The use of an excess amount of TrCl (3.0 mol) affected the yield of **5**, but not the ratio of the yields of **3** to **4**. At lower temperature, the reaction of OH-3 would be sterically disturbed by a branch at C-4 that is oriented to the same side of the furanose ring as OH-3.

Table 1. Temperature Dependence of the Tritylation Reaction of **1**

TrCl (molar amount)	Reaction temperature (°C)	Reaction time (h)	Yield of the trityl ether (%) **2** 6-Tr	**3** 3,6-di-Tr	**4** 5,6-di-Tr	**5** 3,5,6-tri-Tr
2.4	50	20	66	5	26	0
2.4	70	20	36	10	50	1
2.4	95	20	41	19	33	6
2.4	115	20	48	26	12	11
3.0	115	20	41	27	12	18



1 2 3 4 5

Chart 1

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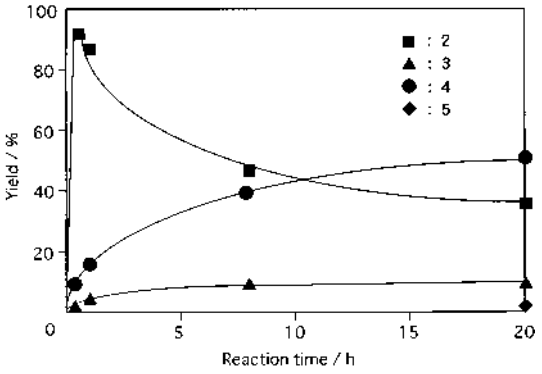

Fig. 1. Time Course of the Tritylation Reaction of **1** with 2.4 Molar Amounts of Trityl Chloride in Pyridine at 70 °C

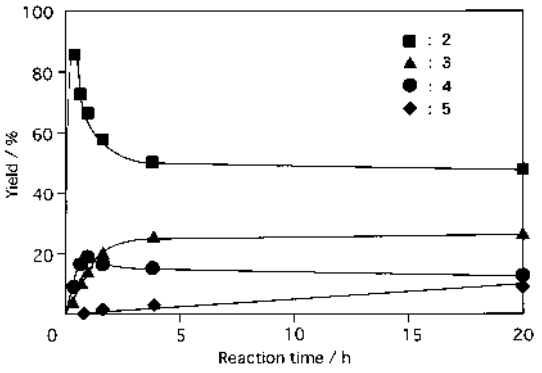

Fig. 2. Time Course of the Tritylation Reaction of **1** with 2.4 Molar Amounts of Trityl Chloride in Pyridine at 115 °C

The increase in the yield of **5** at higher temperatures (5% higher at 95 °C and 10% higher at 115 °C compared to that at 70 °C) was not compatible with the decrease in the yield of **4** (17% lower at 95 °C and 38% lower at 115 °C compared to that at 70 °C); in addition, the yield of **2** increased with the reaction temperature. Therefore, the possibility of a reverse reaction to form **2** should be considered over a longer period.

Observing the reaction mixture, pyridinium chloride formed during the tritylation reaction in pyridine precipitated at 50 and 70 °C, while it did not precipitate throughout the reaction period at 95 and 115 °C. This suggests that pyridinium chloride dissolved in pyridine reacts with a trityl ether to cause the reverse reaction in Eq. 1.[17—19] The trityl ether of OH-6, however, does not react with pyridinium chloride, because no starting material **1** was recovered from any reaction mixture conducted under the reaction conditions shown in Table 1.

$$ROH + TrCl + C_5H_5N \rightarrow ROTr + C_5H_5N \cdot HCl \quad (1)$$

Figures 1 and 2 show the time course of the tritylation reaction at 70 and 115 °C, respectively. The tritylation towards the primary hydroxyl group at C-6 occurs very quickly to give **2**, and in both cases, **2** was gradually consumed as **3** and **4** were produced. The yields of **3** and **4** increased normally with the reaction period at 70 °C (Fig. 1). At 115 °C (Fig. 2), however, the profile of the yield of **4** is obviously different from that of **3**; above the peak of the yield of **4** at 1 h, it gradually goes down to a half value until the end of the reaction period. The decrease would be mainly due to the reverse reaction. The time course of the yields of **2** and **3** reaches a plateau after 4 h, and that of **5** is still increasing (Fig. 2).

The conversion of **4** to **3** by an intramolecular migration of a trityl group can be neglected because of the following experimental facts. The reaction of **4** with 2 mol of pyridinium chloride in pyridine at 115 °C for 20 h gave the degraded compound **2** in 90% yield and a 5% yield of **3** without any recovery of **4**. The reaction of **3** under the same reaction conditions gave **2** in 70% yield and **4** in 3% yield along with 21% recovery of **3**. In both reactions, the yields of the redistributed compounds were extremely low and most of the starting di-*O*-trityl derivatives were converted to the mono-*O*-trityl derivative **2**. The results indicate that OH-5 is much less resistant to the attack of pyridinium cation than OH-3 is, and even though migration might be possible, the reverse reaction continued to predominate. A small amount of the redistributed di-*O*-trityl ether was probably derived from **2** and TrCl, both of which were produced through the reverse reaction.

Besides the di-*O*-tritylation, a valuable fact found was that the mono-*O*-tritylation against the primary hydroxyl group at C-6 occurred rapidly to form **2** which was then consumed to produce **3** and **4** (Figs. 1 and 2). Although selective tritylation against the primary alcoholic function has usually been performed at 50—60 °C for 4—20 h, the yield of **2** conducted at 70 °C for 20 min and that at 115 °C for 10 min was 93 and 86%, respectively.

This article presents another example of the redistribution of a trityl ether among secondary hydroxyl groups, supporting the previous findings.[14] Simultaneous protection of the primary and secondary hydroxyl groups by tritylation could make it possible to prepare partially protected sugar derivatives having a free secondary hydroxyl group such as **3** or **4**. In the protection of hydroxyl groups which include two or more secondary ones, however, the redistribution of trityl groups must be considered, especially for the tritylation at higher reaction temperature.

Experimental

The melting points were determined with a Yanagimoto MP-500D melting-point apparatus and are uncorrected. The optical rotations were measured with a Horiba SEPA-200 polarimeter at 20 °C. The NMR spectra were recorded with a Varian VXR-300 spectrometer at 300 MHz for ^{1}H-NMR and at 75.4 MHz for ^{13}C-NMR. Assignment of all proton and carbon signals was performed based on H–H and C–H COSY measurements. The chemical shifts of the protons were calculated from that of the satellite peak of $CDCl_3$ at δ 7.26, and those of the carbons are relative to the central peak of $CDCl_3$ at δ 77.0 and to the peak of C_5D_5N at δ 150.0. The ^{1}H- and ^{13}C-NMR data are shown in the following section. Column chromatography was performed on silica gel (Wakogel C-300). Thin layer chromatography was performed on Silica gel G 60 (Merck, No. 5721).

Tritylation of 1 A mixture of **1** (220 mg, 1.0 mmol), trityl chloride (669 mg, 2.4 mmol), and pyridine (1.1 ml) was stirred at 50, 70, 95, or 115 °C for each period. The mixture was poured into ice water with stirring, and then extracted with chloroform. The organic layer was washed with 5% hydrochloric acid, 5% sodium hydrogen carbonate, and water successively. The solution was dried over anhydrous sodium sulfate and evaporated to a syrup. Column chromatography using a mixed solvent of toluene and ethyl acetate afforded **5**, **3**, **4**, and **2** successively.

5: $[\alpha]_D$ −44.1° (c=1.0, chloroform). *Anal*. Calcd for $C_{66}H_{58}O_6$: C, 83.69; H, 6.17. Found: C, 83.14; H, 6.26. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, s, $\underline{Me_2}C$), 0.94 (3H, s, $\underline{Me_2}C$), 3.10 (1H, d, $J_{3,4}$=2.7 Hz, H-3), 3.53 (1H, dd, $J_{5,6a}$=2.5 Hz, $J_{6a,6b}$=9.0 Hz, H-6a), 3.55 (1H, d, $J_{1,2}$=3.4 Hz, H-2), 3.63 (1H, dd, $J_{4,5}$=1.0 Hz, H-4), 4.00 (1H, dd, $J_{5,6b}$=7.8 Hz, H-6b), 4.54 (1H, ddd, H-5), 5.38 (1H, d, H-1), 7.07—7.60 (45H, m, 3×$\underline{Ph_3}C$). ^{13}C-NMR ($CDCl_3$) δ: 26.0 ($\underline{Me_2}C$), 26.8 ($\underline{Me_2}C$), 66.2 (C-6), 72.9 (C-5), 79.5 (C-3), 81.7 (C-2),

82.2 (C-4), 87.0 ($Ph_3\underline{C}$), 87.1 ($Ph_3\underline{C}$), 87.3 ($Ph_3\underline{C}$), 103.8 (C-1), 110.7 ($Me_2\underline{C}$).

3: $[\alpha]_D$ −43.4° (c=1.7, chloroform). *Anal*. Calcd for $C_{47}H_{44}O_6$: C, 80.09; H, 6.29. Found: C, 80.00; H, 6.20. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, s, $\underline{Me_2}C$), 1.35 (3H, s, $\underline{Me_2}C$), 2.45 (1H, d, $J_{5,OH}$=6.1 Hz, OH-5), 3.42 (1H, dd, $J_{5,6a}$=3.0 Hz, $J_{6a,6b}$=9.4 Hz, H-6a), 3.53 (1H, dd, $J_{5,6b}$=4.9 Hz, H-6b), 3.66 (1H, d, $J_{1,2}$=3.7 Hz, H-2), 4.03 (1H, d, $J_{3,4}$=3.1 Hz, H-3), 4.30 (1H, dd, $J_{4,5}$=8.8 Hz, H-4), 4.41 (1H, dddd, H-5), 5.74 (1H, d, H-1), 7.20—7.50 (30H, m, 2×$\underline{Ph_3}C$). ^{13}C-NMR ($CDCl_3$) δ: 25.9 ($\underline{Me_2}C$), 26.6 ($\underline{Me_2}C$), 65.1 (C-6), 67.7 (C-5), 77.8 (C-3), 80.4 (C-4), 81.9 (C-2), 86.7 ($Ph_3\underline{C}$), 87.3 ($Ph_3\underline{C}$), 104.4 (C-1), 111.0 ($Me_2\underline{C}$).

4: $[\alpha]_D$ −48.1° (c=1.0, chloroform). *Anal*. Calcd for $C_{47}H_{44}O_6$: C, 80.09; H, 6.29. Found: C, 79.72; H, 6.33. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, s, $\underline{Me_2}C$), 1.51 (3H, s, $\underline{Me_2}C$), 2.80 (2H, d, $J_{5,6}$=5.7 Hz, H-6′s), 4.23 (1H, d, $J_{3,OH}$=3.0 Hz, OH-3), 4.28 (1H, dd, $J_{3,4}$=3.3 Hz, H-3), 4.28 (1H, dt, $J_{4,5}$=4.6 Hz, H-5), 4.53 (1H, d, $J_{1,2}$=3.7 Hz, H-2), 4.54 (1H, dd, H-4), 6.01 (1H, d, H-1), 7.18—7.37 (30H, m, 2×$\underline{Ph_3}C$). ^{13}C-NMR ($CDCl_3$) δ: 26.3 ($\underline{Me_2}C$), 26.8 ($\underline{Me_2}C$), 63.2 (C-6), 73.1 (C-5), 75.7 (C-3), 79.5 (C-4), 85.2 (C-2), 86.9 ($Ph_3\underline{C}$), 88.6 ($Ph_3\underline{C}$), 104.5 (C-1), 111.3 ($\underline{Me_2}C$).

2: mp 142—143 °C, $[\alpha]_D$ −7.2° (c=1.0, chloroform) (lit.[16] mp 141—143 °C, $[\alpha]_D$ −5.0° (c=1, chloroform)). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, s, $\underline{Me_2}C$), 1.48 (3H, s, $\underline{Me_2}C$), 2.82 (1H, d, $J_{5,OH}$=4.2 Hz, OH-5), 3.34 (1H, dd, $J_{5,6a}$=5.9 Hz, $J_{6a,6b}$=9.8 Hz, H-6a), 3.43 (1H, d, $J_{3,OH}$=3.0 Hz, OH-3), 3.45 (1H, dd, $J_{5,6b}$=4.0 Hz, H-6b), 4.12 (1H, dd, $J_{3,4}$=2.7 Hz, $J_{4,5}$=5.8 Hz, H-4), 4.21 (1H, dddd, H-5), 4.31 (1H, dd, H-3), 4.51 (1H, d, $J_{1,2}$=3.7 Hz, H-2), 5.95 (1H, d, H-1), 7.21—7.48 (15H, m, $\underline{Ph_3}C$). ^{13}C-NMR ($CDCl_3$) δ: 26.2 ($\underline{Me_2}C$), 26.8 ($\underline{Me_2}C$), 64.8 (C-6), 70.1 (C-5), 75.8 (C-3), 79.5 (C-4), 85.1 (C-2), 87.1 ($Ph_3\underline{C}$), 104.9 (C-1), 111.6 ($Me_2\underline{C}$).

Acetylation of 3 and 4 Compound **3** (20 mg) was acetylated as usual with acetic anhydride in pyridine to give 5-*O*-acetyl-1,2-*O*-isopropylidene-3,6-di-*O*-trityl-α-D-glucofuranose (**3a**) quantitatively. ^{1}H-NMR ($CDCl_3$) of **3a** δ: 1.08 (3H, s, $\underline{Me_2}C$), 1.42 (3H, s, $\underline{Me_2}C$), 1.85 (3H, s, Ac), 3.53 (1H, dd, $J_{5,6a}$=3.7 Hz, $J_{6a,6b}$=10.5 Hz, H-6a), 3.57 (1H, dd, $J_{5,6b}$=2.2 Hz, H-6b), 3.77 (1H, d, $J_{3,4}$=3.3 Hz, H-3), 4.03 (1H, d, $J_{1,2}$=3.7 Hz, H-2), 4.68 (1H, dd, $J_{4,5}$=8.6 Hz, H-4), 5.52 (1H, ddd, H-5), 5.82 (1H, d, H-1), 7.18—7.48 (30H, m, 2×$\underline{Ph_3}C$). Compound **4** was also converted to 3-*O*-acetyl-1,2-*O*-isopropylidene-5,6-di-*O*-trityl-α-D-glucofuranose (**4a**). ^{1}H-NMR ($CDCl_3$) of **4a** δ: 1.35 (3H, s, $\underline{Me_2}C$), 1.51 (3H, s, $\underline{Me_2}C$), 1.59 (3H, s, Ac), 2.38 (1H, dd, $J_{5,6a}$=2.8 Hz, $J_{6a,6b}$=10.4 Hz, H-6a), 2.96 (1H, dd, $J_{5,6b}$=2.2 Hz, H-6b), 3.87 (1H, ddd, $J_{4,5}$=8.3 Hz, H-5), 4.58 (1H, d, $J_{1,2}$=3.8 Hz, H-2), 5.17 (1H, dd, $J_{3,4}$=3.0 Hz, H-4), 5.29 (1H, d, H-3), 5.83 (1H, d, H-1), 7.09—7.42 (30H, m, 2×$\underline{Ph_3}C$).

Reaction of 3 and 4 with Pyridinium Chloride A mixture of **3** (200 mg, 0.284 mmol), pyridine (1.0 ml), and pyridinium chloride (65.7 mg, 0.568 mmol) was stirred at 115 °C for 20 h. Work-up in the same manner as that for tritylation gave **4** (6 mg, 3%), **3** (41 mg, 21%), and **2** (92 mg, 70%). The reaction of **4** (200 mg) with pyridinium chloride (65.7 mg) in the same reaction conditions as above gave **3** (10 mg, 5%) and **2** (118 mg, 90%).

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