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## Note

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# Nucleophilic displacement of the triflate group in benzyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-trifluoromethanesulfonyl-α-D-mannopyranoside*

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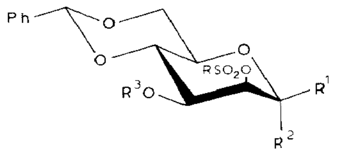
Whereas nucleophilic substitution of a 2-sulfonyloxy group in alkyl 4,6-*O*-benzylidene-β-D-mannopyranoside (**1**) can be effected[1–6], the same reaction in the α series (**2**) is difficult[7] or impossible[1,4–6]. The inertness of the 2-sulfonyloxy group in **2** was explained[1,8] by the unfavourable torsional strain and dipolar interactions developed in the transition state of the displacement reaction. Whereas the *N*-imidazolylsulfonyloxy group in **2** can be displaced by the azide anion to afford 23% of a 2-azido-2-deoxy-α-D-*gluco* derivative[7], the 2-trifluoromethanesulfonate (triflate) group could not be replaced by the fluoride anion[4,6] and only products of elimination were obtained.



**1** $R^1$ = OAlk, $R^2$ = H, $R^3$ = Me, Bzl
**2** $R^1$ = H, $R^2$ = OAlk, $R^3$ = Me, Bzl

In an attempt to shed more light on this displacement reaction, we have investigated the reaction of benzyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-triflyl-α-D-mannopyranoside (**3**) with various nucleophiles. Treatment of benzyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[9] with triflic anhydride and pyridine gave **3** in high yield. The reactions of **3** with nucleophiles (as the tetrabutylammonium or alkali metal salts) were conducted in toluene, *N,N*-dimethylformamide (DMF), or 1:1 *N,N*-dimethylformamide–hexamethylphosphoric triamide (HMPT) until

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TABLE I

THE REACTION OF BENZYL 3-*O*-BENZYL-4,6-*O*-BENZYLIDENE-2-*O*-TRIFLYL-$\alpha$-D-MANNOPYRANOSIDE (**3**) WITH NUCLEOPHILES (RNu)

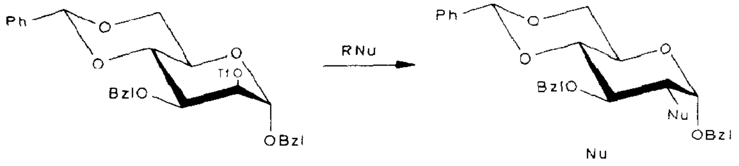
| *Entry No.* | *RNu* | *Solvent* | *Reaction conditions* | *T.l.c. solvent* | *Product* | *Yield (%)* | **5** *Yield (%)* | *Other products* |
|---|---|---|---|---|---|---|---|---|
| 1 | $Bu_4NF$ | DMF–HMPT 1:1 | 50°, 15 h | *B, D* | | | 88 | |
| 2 | CsF | DMF | room temp., 5 days | | | | 95 | |
| 3 | $Bu_4NCl$ | DMF–HMPT 1:1 | 60°, 15 h | *C, E* | **4a** | 10.5 | 11 | **3** 24%, **7** 54% |
| 4 | $Bu_4NCl$ | Toluene | 80°, 5 days | | **4a** | 2.5 | | Decomposition |
| 5 | $Bu_4NOBz$ | Toluene | 110°, 1.5 h | *C, E* | **4b** | 9 | 76 | |
| 6 | $Bu_4NNPhth$ | Toluene | 50°, 48 h | *B, D* | **4c** | 11 | 81 | |
| 7 | $Bu_4NN_3$ | Toluene | 70°, 10 h | *A* | **4d** | 38 | 49 | |
| 8 | $LiN_3$ | DMF | room temp., 12 h | | **4d** | 39 | 44 | |
| 9 | $Bu_4NBr$ | DMF–HMPT 1:1 | 50°, 15 h | *C, E* | **4e** | 26 | 24 | **6** 21%, **7** 24% |
| 10 | $Bu_4NBr$ | Toluene | 70°, 5 h | *C, F* | **4e** | 9.8 | | Decomposition |
| 11 | $Bu_4NCN$ | Toluene | 80°, 8 h | *D* | | | 91 | |
| 12 | $Bu_4NCN$ | DMF–HMPT 1:1 | room temp., 3 h | | | | 100 | |
| 13 | KCN | DMF | 80°, 24 h | | | | 82.5 | |
| 14 | $Bu_4NI$ | Toluene | 110°, 7 h | *A* | **4f** | 79 | | |

t.l.c. showed the disappearance of the substrate to be complete. The products were isolated by chromatography and the results are collected in Table I.

Fluoride anion gave a high yield of benzyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hex-2-enopyranoside (**5**) (entries 1 and 2). The same result was obtained with the cyanide anion (entries 11–13). The reaction with the chloride anion in DMF–HMPT afforded the substitution product **4a** in low yield and larger amounts of two elimination products **5** and **7**. In toluene under more vigorous conditions, decomposition took place and only a small amount of the substitution product was obtained (entry 4). Benzoate, phthalimide, and azide anions afforded increasing yields of the substitution products **4b**–**4d**, respectively (entries 5–7), accompanied by substantial amounts of the elimination product **5**, especially for the bulky phthalimide anion.

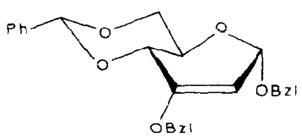
The reaction with bromide anion gave a moderate yield of the substitution product **4e** and the elimination products **5**–**7** in approximately equal yields (entry 9). However, in toluene under more vigorous conditions, the yield of **4e** was low and extensive decomposition was observed (entry 10). The most significant result was achieved with iodide ion, which gave **4f** in high yield (entry 14).

The data in Table I, except for entries 4 and 10, show 80–90% conversion of **3** into defined products, and the different reaction conditions did not change substantially the outcome of the reactions (*cf.* entries 1–2, 7–8, and 10–12). It is concluded that the foregoing results demonstrate that, in spite of steric and electrostatic factors[1,8], good nucleophiles can effect normal substitution reactions in **3**. On the other hand, since the leaving group at C-2 and H-3 are ideally suited for the elimination reaction, strongly basic (*e.g.*, cyanide) and bulky anions (*e.g.*,

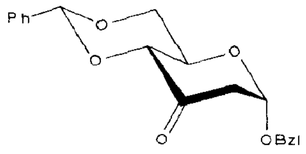


**3**

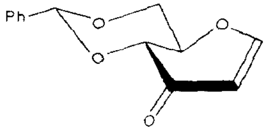
| | Nu |
|---|---|
| **4a** | Cl |
| **4b** | OBz |
| **4c** | NPhth |
| **4d** | $N_3$ |
| **4e** | Br |
| **4f** | I |



**5**



**6**



**7**

phthalimide) cause elimination reactions. Thus, there is a balance between the nucleophilicity, basicity, and steric demands of the anions employed. The first two factors appear to be more important, since azide displacement of the 2-sulfonyloxy group in the non-rigid system of methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside led to 2-azido-2-deoxy-α-D-*gluco* derivative in yields of 27[10] and 37%[7] only (*cf.* Table I, entries 7 and 8). Although the substitution reaction in the *β-manno* system is facile, nevertheless the elimination reaction is an important side-process[6].

The enol ether **5** is relatively stable at room temperature, but, on heating a solution in toluene, it loses the 3-*O*-benzyl group and yields the 2-deoxy-3-ulose derivative **6**. This compound is unstable and readily loses a molecule of benzyl alcohol to give the known[11] αβ-unsaturated ketone **7**.

## EXPERIMENTAL

*General methods.* — Melting points are uncorrected. Optical rotations were measured at ~20° with a Perkin–Elmer 141 polarimeter. N.m.r. spectra were recorded with a Bruker WH 300 or WH 400 spectrometer. T.l.c. was performed on Silica Gel HF-254 and column chromatography on silica gel 200–300 mesh (Merck), using *A*, 9:1 chloroform–hexane; *B*, 4:1 dichloroethane–hexane; *C*, 7:3 chloroform–hexane; *D*, 9:1 ether–pentane; *E*, 9:1 toluene–acetone; *F* 9:1 chloroform–acetone. All reagents and solvents used were dry, and all reactions were performed under argon.

Analytical and spectral data for **3**–**7** are collected in Tables II and III, respectively.

*Benzyl 3-O-benzyl-4,6-O-benzylidene-2-O-trifluoromethanesulfonyl-α-D-mannopyranoside* (**3**). — To a stirred solution of pyridine (0.94 mL, 11.63 mmol) and triflic anhydride (1.64 mL, 10 mmol) in dichloroethane (40 mL) at −15° was added a solution of benzyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[9] (2.24 g, 5 mmol) dropwise, and stirring was continued for 1 h at room temperature. After addition of saturated aqueous $NaHCO_3$, the mixture was stirred for 0.5 h, and the organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated. Column chromatography (solvent *D*) of the residue gave **3** (2.74 g, 92%).

*Reaction of* **3** *with the nucleophiles shown in Table I.* — *Procedure A.* In a typical experiment, a solution of 1 mmol of **3** in dry toluene (5 mL) was treated with 3 mmol of $Bu_4N^+Nu^-$ at 50° →reflux until the reaction was complete (t.l.c.). The solvent was then evaporated under reduced pressure and the products were isolated by column chromatography.

*Procedure B.* A solution of **3** (1 mmol) and $Bu_4N^+Nu^-$ (5 mmol) in 1:1 DMF–HMPT (5 mL) was stirred at 50–60° until disappearance of the substrate was complete (t.l.c.), then poured into ice–water, and extracted 3 times with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$ and then with

TABLE II

PHYSICAL AND ANALYTICAL DATA FOR **3–7**

| Compound No. | M.p. (°) | $[\alpha]_D$ (°) (CHCl$_3$) | Formula | Calc. | | | Found | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | Other | C | H | Other |
| **3** | 100.5–101 | +32 (*c* 0.9) | $C_{28}H_{27}F_3O_8S$ | 57.93 | 4.69 | F, 9.81 | 57.89 | 4.49 | F, 9.80 |
| **4a** | 152–154 | +34 (*c* 0.95) | $C_{27}H_{27}ClO_5$ | 69.45 | 5.83 | Cl, 7.54 | 69.49 | 6.23 | Cl, 7.56 |
| **4b** | 70–71 | +130 (*c* 1.9) | $C_{34}H_{32}O_7$ | 73.89 | 5.84 | | 73.33 | 5.71 | |
| **4c** | syrup | +108 (*c* 1) | $C_{35}H_{31}NO_7$ | 72.77 | 5.41 | N, 2.42 | 73.01 | 5.93 | N, 2.41 |
| **4d** | 132–134 | +59 (*c* 1.9) | $C_{27}H_{27}N_3O_5$ | 68.48 | 5.75 | N, 8.81 | 68.55 | 5.56 | N, 8.64 |
| **4e** | 158–159 | +90 (*c* 1.1) | $C_{27}H_{27}BrO_5$ | 63.41 | 5.32 | Br, 15.62 | 63.90 | 5.65 | Br, 15.06 |
| **4f** | 169–170 | +121 (*c* 1.9) | $C_{27}H_{27}IO_5$ | 58.07 | 4.87 | I, 22.72 | 57.78 | 4.84 | I, 22.51 |
| **5** | 173–173.5 | +67 (*c* 1.1) | $C_{27}H_{26}O_5$ | 75.33 | 6.09 | | 75.01 | 6.29 | |
| **6** | 154–155 | +62 (*c* 0.4) | $C_{20}H_{20}O_5 \cdot H_2O$ | 67.02 | 6.19 | | 67.13 | 6.33 | |
| **7**[a] | 127–128 | +187 (*c* 1.4) | $C_{13}H_{12}O_4$ | 67.23 | 5.21 | | 67.15 | 5.08 | |

[a] Lit.[11] m.p. 128–129°, $[\alpha]_D$ +189°.

TABLE III

$^1$H-N.M.R. DATA FOR **3**–**7**

| *Compound* | *Chemical shifts (δ, p.p.m.)* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *H-1* | *H-2* | *H-3* | *H-4* | *H-5* | *H*-6a | *H*-6e | *ϕCH* | *ϕCH$_2$* |
| **3** | 5.03 | 5.10 | 4.10 | 4.05 | 3.89 | 3.84 | 4.22 | 5.62 | 4.78, 4.42 |
| **4a** | 5.02 | 3.95 | 4.03 | 3.67 | 4.07 | 3.77 | 4.27 | 5.59 | 4.87, 4.72 |
| **4b** | 5.25 | 5.15 | 4.29 | 3.81 | 4.04 | 3.81 | 4.30 | 5.64 | 4.84, 4.64 |
| **4c** | 4.97 | 4.40 | 5.43 | 3.79 | 4.13 | 3.82 | 4.29 | 5.63 | 4.82, 4.60 |
| **4d**[a] | 4.97 | 3.40 | 4.14 | 3.59 | 3.81 | 3.62 | 4.23 | 5.56 | 4.87, 4.67 |
| **4e** | 5.03 | 3.97 | 4.10 | 3.66 | 4.03 | 3.76 | 4.25 | 5.58 | 4.86, 4.69 |
| **4f** | 5.04 | 4.04 | 4.10 | 3.68 | 4.04 | 3.78 | 4.27 | 5.60 | 4.87, 4.68 |
| **5**[b] | 4.78 | 5.25 | | 4.28 | 4.27–4.15[e] | 3.80 | 4.27–4.15 | 5.59 | 4.87, 4.69 |
| **6**[c] | 4.73 | 2.10 | (H-2*a*) | 3.65 | 4.10 | 3.50 | 4.01 | 5.28 | 4.31 |
| | | 2.40 | (H-2*e*) | | | | | | |
| **7**[d] | 7.3[f] | 5.41 | | | | | 3.8 | 5.61 | |

| | *Coupling constants (Hz)* | | | | | | |
|---|---|---|---|---|---|---|---|
| | $J_{1,2}$ | $J_{2,3}$ | $J_{3,4}$ | $J_{4,5}$ | $J_{5,6a}$ | $J_{5,6e}$ | $J_{6a,6e}$ |
| **3** | 1.5 | 3.1 | 9.9 | 9.9 | 10.2 | 4.4 | 9.7 |
| **4a** | 3.5 | 9.8 | 9.5 | 9.0 | 10.0 | 5.0 | 10.0 |
| **4b** | 3.9 | 9.7 | 9.5 | 9.6 | 10.0 | 4.5 | 10.5 |
| **4c** | 3.5 | 11.0 | 9.1 | 9.1 | 9.8 | 4.8 | 10.2 |
| **4d** | 3.5 | 9.9 | 9.9 | 9.5 | 10.0 | 5.0 | 10.0 |
| **4e** | 3.4 | 10.1 | 9.0 | 9.0 | 10.2 | 5.0 | 10.8 |
| **4f** | 3.7 | 10.0 | 10.0 | 9.0 | 10.2 | 4.8 | 10.2 |
| **5** | 3.0 | | | 8.5 | 11.6 | | |
| **6** | 4.8[g] | | | 10.0 | 10.2 | 4.9 | |
| | 3.2[h] | | | | | | |
| **7** | 6.0 | | | | | | |

[a] $\nu_{max}$ 2110 cm$^{-1}$ ($N_3$). [b] $\nu_{max}$ 1655 cm$^{-1}$. $^{13}$C-N.m.r. data: δ 154.6 (C-3), 102.2 (benzylidene CH), 95.9, 95.7 (C-1, C-2), 75.0 (C-4), 70.0, 69.4, 69.0 (2 $CH_2Ph$, C-6), 63.8 (C-5). [c] $\nu_{max}$ 1710 cm$^{-1}$. [d] $\nu_{max}$ 1710 and 1600 cm$^{-1}$; $^1$H-n.m.r. data are in full agreement with the literature values[11]. [e] Together with H-6*e*. [f] Together with aromatic protons. [g] $J_{1,2a}$. [h] $J_{1,2e}$; $J_{2a,2e}$ 14.5 Hz.

brine, dried ($MgSO_4$), and concentrated. The products were isolated by column chromatography.

*Procedure C.* A solution of **3** (1 mmol) and $M^+Nu^-$ (10 mmol) in DMF (5 mL) was stirred at room temperature →80°. The products were then isolated as in procedure *B*.

## ACKNOWLEDGMENTS

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