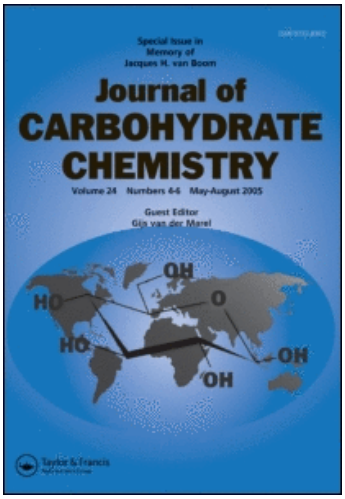

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Use of Trifluoromethanesulfonic Acid in Fischer Glycosylations

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COMMUNICATION

USE OF TRIFLUOROMETHANESULFONIC ACID IN FISCHER GLYCOSYLATIONS

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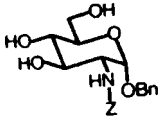
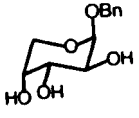
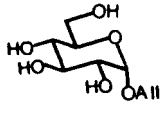
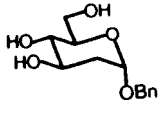
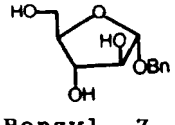
The Fischer glycosylation[1] is one of the standard reactions in carbohydrate chemistry, in which a reducing sugar is reacted under acid catalysis with a simple alcohol to give a glycoside. Hydrochloric acid is the classical catalyst, but other proton, Lewis acid, or acid form ion exchange resins have also been used. Now, the use of trifluoromethanesulfonic acid (triflic acid) as a catalyst is communicated.[2]

Generally, the use of triflic acid in Fischer glycosylations gave comparable (Table 1, entry 1 and 2) or superior results as compared to literature data. Thus, in the preparation of allyl D-glucopyranosides a favourable 3:1 α/ß-mixture (as judged by GC and NMR integration) was obtained even at low acid concentrations; using concentrated sulfuric acid as catalyst an α/ß=2:1 equilibrium mixture was formed.[6] The α-glycoside was not isolated but benzylidenated[7] to

TABLE 1

Reactions Conditions and Yields for some Glycosides

Entry[a]	Product	Reducing Sugar	Alcohol	CF_3SO_3H	Conditions	Yield [%] obtained	reported
1		470 g	6 l	100 ml	0°→RT, 90h	59-61[b]	57[4]
2		5 g	200 ml	2.3 ml	0°→80°C, 2.5h	90[b]	91[5]
3		1 kg	2.5 l	8 ml	0°→80°C, 48h	67 (GC)[c]	
4		0.5 g	25 ml	0.04 ml	0°→RT, 90h	82	58[8]
5		5 g	250 ml	0.2 ml	0°→50°C, 195min	28[c]	c

a. Bn = Benzyl, Z = Benzyloxycarbonyl, All = Allyl, RT = room temperature
b. Physical constants were in accordance with those reported
c. see text for discussion

give 33% of allyl 4,6-O-benzylidene-α-D-glucopyranoside. Benzylation of 2-deoxyglucose gave good yields of benzyl 2-deoxy-α-D-arabino-hexopyranoside (Table 1, entry 4). In this reaction it was important to use purified benzyl alcohol, because small amounts of otherwise formed benzyl 4,6-O-benzylidene-2-deoxy-α-D-arabino-hexopyranoside hampered the crystallization of the desired product decreasing the yield. Notably, furanosides but practically no pyranosides could be obtained upon benzylation of D-arabinose under kinetic control.[11] Benzyl α-D-arabinofuranoside (Table 1, entry 5), which had been synthesized before[12] via the "benzoate route"[13] from 2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl bromide[14] in 50% yield, could be isolated by column chromatography as the major product, but preferably the crude reaction mixture was further processed to facilitate purification. For our purposes the crystalline 5-O-tosyl derivative was prepared.

EXPERIMENTAL

General Methods. Solvents and reagents were obtained from Fluka (puriss. p.a.). Evaporation: Büchi rotary evaporator. TLC: precoated silica gel 60F-254 plates (Merck), detection by UV light (254 nm) and spraying with a 10% solution of conc. H_2SO_4 in MeOH followed by heating. Column chromatography: silica gel (63-200 µm, Merck). GC: All samples were fully silylated with N,O-bis-trimethysilyl-trifluoroacetamide/pyridine; Dani 3800, injector temp. 40-280 °C, 15 m capillary column PS 086 (12-15% phenylmethylsilicone), FI detection. ^{1}H-NMR:Bruker AS 250 (250 MHz), Bruker HX-270 (270 MHz), or Bruker WM 400 (400 MHz), chemical shifts in ppm relative to tetramethylsilane as internal standard. MS:MS 9 updated with Finnagan ZAB

console, data system SS 200, VG Altrinchem (EI:70 eV); MM 7070 F, data system 2050, VG Altrinchem (CI:NH_3).

General Procedure for Glycosylation Reactions. To a suspension of the reducing sugar in benzyl or allyl alcohol was added triflic acid at 0-5 °C (cf. Table 1) either via a syringe directly into the suspension or dropwise as a solution in the respective alcohol. After the reaction mixture was warmed to room temperature or up to 80 °C the course of the reaction was followed by TLC and/or GC. Reactions were terminated by addition of triethylamine and concentrated under reduced pressure.

Allyl 4,6-O-benzylidene-α-D-glucopyranoside. The crude reaction mixture (Table 1, entry 3; 1.318 kg) containing 67.2% α- and 21.2% ß-anomer by GC was benzylidenated with benzaldehyde/zinc chloride as described.[7] The reaction mixture was poured into a vigorously stirred hexane/dilute sodium bicarbonate solution. The crystals formed were washed with water/hexane and recrystallized once from ethanol to give 565 g (33%) of pure title compound: mp 133-134 °C (lit[7]:25%, mp 130-131 °C); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.53-7.46 (2H, m, aromatic), 7.40-7.33 (3H, m, aromatic) 5.53 (s, C<u>H</u>Ph), 4.94(d, 1-H, $J_{1,2}$=3.9 Hz), 4.78 (dd, 6a-H, $J_{5,6a}$=4.7 Hz,$J_{6a,6b}$=10.2 Hz), 3.94 (dd~t, 3-H, $J_{2,3}$~10.0 Hz), 3.86 (ddd~dt,5-H, $J_{4,5}$= 8.9 Hz), 3.37 (dd~t, 6b-H, $J_{5,6b}$=10.5 Hz), 3.62 (1H, m, 2-H), 3.49 (dd~t, 4-H, $J_{3,4}$~9.0 Hz), 3.00 (s_{br}, 3-O<u>H</u>), 2.42 (d_{br}, 2-O<u>H</u>, $J_{2,2\text{-}OH}$~8 Hz), allyl:5.93 (dddd), 5.33 (dddd~dq), 5.29 (dddd~dq), 4.25 (dddd~ddt), 4.05 (dddd~ddt). EI-MS:308 (5,$M^{+\cdot}$), 307 (5,$M^{+\cdot}$-H), 251 (5, $M^{+\cdot}$-O All), 107 (100, $PhCHOH^+$), 105 (80, $PhCO^+$), 41(64, All^+).

Benzyl 2-deoxy-α-D-arabino-hexopyranoside. Crude glycosylation product (cf. Table 1, entry 4) was crystallized from ethyl acetate/hexane to give 634 mg (82%) of colourless crystals, mp 128-129 °C (lit[8] 58%, mp

129 °C). $[\alpha]_D^{20}$ + 128° (c 0.5, dioxane) (lit[8] $[\alpha]_D^{20}$ + 93° (c 1, H_2O)). The NMR spectrum is in accord with the reported data.[8]

Anal. Calcd for $C_{13}H_{18}O_5$ (254.28):C, 61.41; H, 714. Found: C, 61.39; H, 7.19.

If non-analytical grade benzyl alcohol was used in the reaction, up to 8% of benzyl 4,6-O-benzylidene-2-deoxy-α-D-arabino-hexopyranoside was obtained as by-product upon chromatography (ethyl acetate/methanol 49:1) of the crude glycosylation product. After one crystallization from ether/hexane the compound had mp 147 °C (lit[9] 145-146 °C, lit[10] 138-139 °C): ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 7.49-7.42 (2H, m, aromatic), 7.40-7.31 (8H, m, aromatic), 5.63 (s, CHPh), 5.19 (d, 3-OH, $J_{1,2a}$=3.6 Hz, $J_{1,2e}$ < 1 Hz). 4.64 (d, CH_aH_bPh, $J_{Ha,Hb}$=11.9 Hz), 4.45 (d, CH_aH_bPh), 4.13 (dd, 6a-H, $J_{5,6a}$=4.0 Hz, $J_{6a,6b}$=9.2 Hz), 3.86 (dddd~ddt, 3-H, $J_{3,4}$=9.5 Hz), 3.72 (dd~t, 6b-H), 3.64 (ddd~dt, 5-H), 3.44 (dd~t, 4-H, $J_{4,5}$~8.7 Hz), 2.05 (dd, 2e-H, $J_{2e,3}$= 5.0 Hz, $J_{2a,2e}$=13.1 Hz), 1.66 (ddd, 2a-H, $J_{2a,3}$=11.2 Hz); EI-MS 342 (2.5, $M^{+\cdot}$), 341 (2, $M^{+\cdot}$-H), 251 (0.6, $M^{+\cdot}$-Bn·), 234 (0.6, $M^{+\cdot}$-BnOH), 233 (0.6, $M^{+\cdot}$-Bn·-H_2O), 91 (100, Bn·).

Benzyl α-D-arabinofuranoside. The crude glycosylation product (cf. Table 1, entry 5, 10.4 g, GC:α 44.8%, ß 24.1%) was chromatographed (ethyl acetate/methanol 97.5:2.5) to give 2.25 g (28%) of pure title compound as a syrup: $[\alpha]_D^{20}$ + 122° (c 0.2, dioxane) (lit[12] $[\alpha]_D^{20}$ + 100° (c 2.1, H_2O)); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.40-7.30 (5H, m, aromatic), 5.08 (s, 1-H) 4.75 (d, CH_aH_bPh, J=11.7 Hz), 4.53 (d, CH_aH_bPh), 4.28 (1H, s_{br}, OH). 4.16 (ddd~dt, 4-H), 4.04 (2H, m, H-2, H-3), 3.87 (dd, 5a-H, $J_{4,5a}$=2.2 Hz, $J_{5a,5b}$=11.9 Hz), 3.78 (d_{br}, 5b-H, $J_{4,5b}$~1.5 Hz), 3.25 (2H, ~d, OH); CI-MS 258 (100, $M^{+\cdot}+NH_4^+$), 240 (60, $M^{+\cdot}$ or 258- H_2O).

Anal. Calcd for $C_{12}H_{16}O_5$ (240.255):C, 59.99; H, 6.71. Found: C, 59.60; H 6.67.

Alternatively, a solution of the crude glycosylation product in dichloromethane/pyridine 1:1 (40 ml) was tosylated by addition of p-toluenesulfonyl chloride (8.8 g, 45.6 mmol) in dichloromethane (35 ml) at 0 °C. After completed addition the reaction mixture was left at RT for 26 h. Dichloromethane was evaporated at low temperature, and the product was extracted from ice/water with ethyl acetate. Chromatography (ethyl acetate/hexane 1:1) of the crude tosylates (8.27 g) and crystallization of the main fraction from ethyl acetate/hexane gave pure benzyl 5-O-p-toluenesulfonyl-α-D-arabinofuranoside (2.76 g, 21%): mp 88-89 °C; $[\alpha]_D^{20}$ 83.8° (c 0.5, dioxane); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.81-7.79 (2H, m, aromatic), 7.36-7.29 (7H, m, aromatic), 5.03 s (1-H), 4.72 (d, CH_aH_bPh, $J_{Ha,Hb}$=11.7 Hz), 4.49 (d, CH_aH_bPh), 4.27-4.17 (3H, m, H-4, H-5), 4.10 (dd~d, 2-H, $J_{2,3}$~ 1Hz), 3.90 (ddd~d, 3-H), 2.81 (d, 3-OH, $J_{3,3\text{-OH}}$=9.9 Hz), 2.45 (3H, s, $PhCH_3$), 2.41 (d, 2-OH, $J_{2,2\text{-OH}}$=6.9 Hz); CI-MS 412 (5, $M^{\cdot}+NH_4^+$).

Anal. Calcd for $C_{19}H_{22}O_7S$ (394.422):C, 57.68; H, 5.62; S 8.13, Found: C, 57.75; H 5.62; S 8.01.

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