Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

DISPLACEMENT OF CARBOHYDRATE SULFONATES WITH HALIDE IONS OF TOLUENE-SOLUBILIZED HALIDES

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(Received January 19th, 1970; in revised form, April 8th, 1970)

ABSTRACT

Hexamethylphosphoramide was found to solubilize lithium halides in toluene. Nucleophilic displacement of carbohydrate sulfonates with these toluene-solubilized halide ions produced in excellent yield and short reaction times the corresponding deoxyhalocarbohydrate. With iodide, bromide, and chloride ions a primary methanesulfonate needed respectively 0.25, 1, and 4h for the displacement. Isolated yields exceeded 70%. Displacement of secondary sulfonates was shown to occur with the solubilized halide ions.

INTRODUCTION

Nucleophilic displacement of sulfonic esters of carbohydrates constitutes a well-known method for preparing carbohydrate derivatives[1,2]. In general, primary sulfonates are readily displaced with sodium iodide at 100 to 110° in acetone (sealed tube), whereas secondary sulfonates do not react[2]. This selective displacement was the basis of the Oldham–Rutherford method[3] for distinguishing primary from secondary hydroxyl groups. High-boiling, aprotic solvents of high dielectric constant, such as *N,N*-dimethylformamide and methyl sulfoxide, have not only eliminated the need for sealed tubes for displacement reactions on sulfonates, but have also led[4,5] to instances of displacements on secondary sulfonates when the reactions were carried out at 140 to 150°. However, the displacement of secondary sulfonates has not been uniformly successful[5]; a deep-seated rearrangement has been reported[6].

The preparation of halogenated carbohydrates by sulfonate displacement has been generally restricted to iodides[1a,2]. Although other halides[7] have been used in sulfonate displacement, the yields were not so good as with iodides. Some other procedures[8] for preparing chloro- or bromo-deoxy carbohydrates, not involving sulfonic ester displacements, have been reported. The procedure described here involves displacement of sulfonic esters by toluene-solubilized lithium halides.

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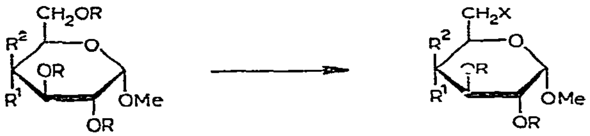
RESULTS AND DISCUSSION

Although other workers[4,5,9] have demonstrated the effectiveness of dipolar, aprotic solvents in carbohydrate synthesis, the high boiling point of these solvents makes their removal difficult and their high dielectric constants overpower the activity of adsorbents making chromatographic monitoring of a reaction difficult. In an attempt to retain the desired solvation properties of these aprotic solvents but decrease the unwanted problems, solutions of metal halides in aprotic solvents were diluted with inert solvents.

With hexamethylphosphoramide [$(Me_2N)_3PO$, HMPA] it was observed that lithium chloride, bromide, and iodide were appreciably solubilized* in toluene (and benzene) when the molar ratio of salt–HMPA was ~1:1. Exploratory experiments determined that these solutions of solubilized lithium halide caused displacement of primary sulfonyloxy groups, and as expected, the rate of halide incorporation was related qualitatively to the halide–sulfonate ratio.

When methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside **1a** and lithium halide-HMPA (~1:1 molar ratio) in a ~1:6 sulfonate–halide molar ratio were heated to reflux in toluene, t.l.c. monitoring showed that with chloride, bromide, and iodide the displacement was essentially complete in 7, 1, and 0.25 h. Work-up and recrystallization gave 70, 77, and 83%, respectively, of isolated deoxyhalocarbohydrate **3-Cl**, **3-Br**, and **3-I** (additional material could be recovered from the mother liquor).



Compound	R	R^1	R^2	R^3
1a	Ac	OAc	H	Ts
1b	H	OH	H	Ts
10a	Ac	OAc	H	H
10b	H	OH	H	H
2	Bz	OMs	H	Ms
11	Bz	OTs	H	Ts

Compound	R	R^1	R^2	Halogen (X)
3	Ac	OAc	H	F, Cl, Br or I
4	H	OH	H	F
5	Bz	OMs	H	Cl, Br or I
6	Bz	H	Br	Br
7	Bz	Br	H	Br
8	Bz	H	I	I
9	Bz	I	H	I

Neither lithium nor sodium fluoride was solubilized in toluene by HMPA. When tetraethylammonium fluoride was suspended in toluene, HMPA added (1:1 molar ratio), and the mixture heated to reflux, a reddish-brown layer separated as the reflux temperature was reached. With the addition of **1a** and continued heating under reflux, t.l.c. monitoring revealed after 9 h three major spots: starting material (**1a** R_F 0.26), one faster moving (R_F 0.31), and one slower moving (R_F 0.19). The syrupy reaction product was catalytically deacetylated with sodium methoxide–

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*The solubilizing effect of HMPA on metal halides has been previously noted[10].

methanol to give a syrup that by cellulose-column chromatography gave **10b**, **1b**, and **4** in 43, 33, and 12% yields, respectively. Since **3-Cl**, **3-Br**, and **3-I** migrated faster than **1** on t.l.c., the spot having R_F 0.31 was presumed to be **3-F** and the spot having R_F 0.19, **10a**. Traces of water led to **10a**; as tetraethylammonium fluoride is extremely hygroscopic, it is difficult to carry out the reaction under rigorously dry conditions. Although the yield of **4** is not outstanding, the literature reports[11] a yield less than 3% overall in a seven-step sequence from D-glucose.

Displacement[12] of a primary sulfonate group in the presence of a secondary one occurs readily. When methyl 2,3-di-*O*-benzoyl-4,6-di-*O*-(methylsulfonyl)-α-D-glucopyranoside (**2**) and lithium halide–HMPA (~1:1 molar ratio) in ~1:6 sulfonate–halide molar ratio were heated to reflux in toluene, in was established (t.l.c.) that with chloride, bromide, and iodide, displacement was essentially complete in 4, 1, and 0.25 h, respectively. Work-up and recrystallization gave 86, 84, and 74% isolated yields, respectively, of the deoxyhalosulfonyloxy derivatives **5-Cl**, **5-Br**, and **5-I**, and additional material could be recovered from the mother liquors.

Trace spots on the t.l.c. plates in the bromide and iodide displacement reactions appeared from their R_F values to be dideoxydibromo- and dideoxydiiodo derivatives, resulting from displacement of the secondary sulfonate group. When **2** reacted with lithium bromide–HMPA in boiling toluene for 116 h, it was observed (t.l.c.) that **2** was transformed into **5-Br** and thence into **6** (or **7**). Work-up of the reaction gave a product, m.p. 124–131°, isolated in 23% yield that gave a correct analysis for a methyl di-*O*-benzoyldibromodideoxyhexoside. This product was shown by multiple-ascent t.l.c. to be a mixture consisting of a major, faster-moving product and a minor, slower-moving one.

Dry-column chromatography[13] provided sufficient separation to allow identification of the major component as **6**, m.p. 133–135°, $[\alpha]_D^{24}$ +156°. N.m.r. spectroscopy showed the H-4 resonance (δ ~4.84) as an ill-defined peak having $J_{3,4}$ and $J_{4,5}$ both less than 3 Hz; in addition the H-5 signal (δ 4.20) was a triplet having a splitting of *ca.* 7 Hz. Several D-galactose derivatives[8d,14] show such a triplet for H-5. Sufficient material could not be obtained to identify the minor product, but it was assumed to be **7** (see below).

Displacement[15] of the *p*-tolylsulfonyloxy groups in **11** by sodium iodide in boiling *N*,*N*-dimethylformamide produced a mixture of **8** and **9**. Extended heating (~20 h) of small-scale reactions of **2** or **5-I** with lithium iodide–HMPA gave (t.l.c.) products chromatographically identical with **8** and **9**.

Work is now in progress to establish the scope of the lithium halide–HMPA reagent in displacing secondary sulfonates.

EXPERIMENTAL

General. — T.l.c. was performed on Silica Gel G* with air-equilibrated plates

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*The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

of 0.25-mm thickness and with solvent systems as specified. The spots were detected by spraying with 5% ethanolic sulfuric acid and heating until charred. Linear, horizontal-paper chromatography was carried out on Schleicher and Schüll 2043b paper with a solvent system BuOH–isoPrOH–H_2O 3:1:1 (v/v). The spots were detected by either the periodate–permanganate spray of Lemieux and Bauer[16] or the $AgNO_3$–NaOH dipping reagent of Smith[17]. U.v. spectra were measured with a Cary Model 14 spectrophotometer. I.r. spectra were determined with a Perkin–Elmer Model 621 spectrophotometer. N.m..r spectra were obtained with a Varian Model HA-100 spectrometer and chemical shifts were compared against internal tetramethylsilane. Melting points of samples in capillary tubes were measured on a Mel-Temp or Mettler FP 1 apparatus. Analytical samples were dried in the presence of sodium hydroxide and sulfuric acid at room temperature in a 1–10-mm vacuum for 24–48 h.

Procedure for sulfonate displacement with **1a**. — Toluene, HMPA, lithium halide, and **1** (see Table I for quantities) were heated to reflux with stirring for the time specified. After cooling the reaction mixture in an ice bath, it was extracted with three 50-ml portions of water, and the organic layer was dried ($MgSO_4$) and concentrated either to a solid or to a syrup that soon turned solid. Recrystallization from 95% ethanol gave the compounds specified in Table I. Physical constants for **3**, **4**, and **5** were in good agreement with values previously reported:

TABLE I

DISPLACEMENT REACTIONS ON PRIMARY SULFONATES

Starting Compound	*X*	*Sulfonate (g)*	*LiX (g)*	*Volume (ml)*		*Reaction time (h)*	*% Yield, after recryst.*	*M.p. (°)*	*Compound isolated*
				HMPA[a]	*Toluene*				
1a	Cl	2.52	1.35	7.0	250	7	70	98–99	**3-Cl**
	Br	4.15	4.6	15.0	250	1	77	116–117	**3-Br**
	I	3.36	5.7	8.0	250	0.25	83	147–149	**3-I**
2	Cl	5.00	1.52	7.0	350	4	86	163–164.5	**5-Cl**
	Br	3.51	3.40	8.0	350	1	84	180 (dec.)	**5-Br**
	I	2.00	3.15	5.0	350	0.25	74	188–191	**5-I**

[a] HMPA = hexamethylphosphoramide.

3-Cl: m.p. 98–99°; $[\alpha]_D^{23}$ +160° (*c* 0.13, chloroform) lit.[18] m.p. 98–99°; $[\alpha]_D^{18}$ +163.8°).

3-Br: m.p. 116–117°; $[\alpha]_D^{24}$ +128° (*c* 0.20, chloroform) (lit.[19] m.p. 115–117.5°; $[\alpha]_D^{19}$ +131.1°).

3-I: m.p. 147–149°; $[\alpha]_D^{24}$ +110° (*c* 0.11, chloroform) (lit.[20] m.p. 150–151°; $[\alpha]_D^{24}$ +116°).

Additional material could be obtained by reworking the filtrates.

Procedure for sulfonate displacement with **2**. — Toluene, HMPA, and lithium halide (see Table I for quantities) were heated to reflux with stirring and *ca.* 100 ml of solvent was distilled off. The mixture was cooled slightly and **2** was added in one portion. The mixture was reheated to reflux for the time specified. The mixture, after cooling in an ice bath, was extracted with three 50-ml portions of water. The organic layer was dried ($MgSO_4$) and concentrated to a syrup, which solidified after 1–2 h. Recrystallization from 95% ethanol gave the products listed below:

5-Cl: m.p. 163–164.5°; $[\alpha]_D^{23}$ +152° (*c* 0.112, chloroform); R_F 0.63 benzene–ethyl acetate 10:1 v/v; λ_{max} in 95% ethanol 275 (ε 1950), 282 nm (1600); λ_{max}^{KBr} 1730 (benzoic ester), 1360, 1185 (sulfonate), 725, 705 cm^{-1} (aryl); n.m.r. data 3.43 (OMe), 2.84 δ (OMs).

Anal. Calc. for $C_{22}H_{23}ClO_9S$: C, 52.96; H, 4.64; Cl, 7.10. Found: C, 52.24; H, 4.84; Cl, 7.03.

5-Br: m.p. 180° dec.; $[\alpha]_D^{25}$ +155° (*c* 0.142, chloroform); R_F 0.68 benzene–ethyl acetate 10:1 v/v; λ_{max} in 95% ethanol 276 (ε 2100), 282 nm (1700); λ_{max}^{KBr} 1730 (benzoic ester), 1355, 1175 (sulfonate), 725, 709 cm^{-1} (aryl); n.m.r. data 3.46 (OMe), 2.86 δ (OMs).

Anal. Calc. for $C_{22}H_{23}BrO_9S$: C, 48.62; H, 4.26; Br, 14.70, S, 5.90. Found: C, 48.74; H, 4.60; Br, 14.13; S, 5.85.

5-I: m.p. 188–191°, $[\alpha]_D^{25}$ +128° (*c* 0.094, chloroform); R_F 0.47 benzene–ethyl acetate 25:1 v/v; λ_{max} in 95% ethanol 275 (ε 2100), 282 nm (1650); λ_{max}^{KBr} 1730 (benzoic ester), 1355, 1175 (sulfonate), 720, 710 cm^{-1} (aryl); n.m.r. data 3.46 (OMe), 2.82 δ (OMs).

Anal. Calc. for $C_{22}H_{23}IO_9S$: C, 44.75; H, 3.92; I, 21.49; S, 5.43. Found: C, 44.63; H, 4.33; I, 21.63; S, 5.26.

Additional product could be obtained by reworking the filtrates.

Methyl 6-deoxy-6-fluoro-α-D-glucopyranoside (**4**). — In an oven-dried flask was placed **1a** (2.2 g), tetraethylammonium fluoride (1.0 g, Eastman Kodak), HMPA (1.5 ml), and anhydrous toluene (100 ml). The mixture was heated for 9 h at reflux with stirring (drying tube on condenser), during which time the suspended solid liquefied and the reaction mixture turned reddish brown. T.l.c. monitoring (benzene–ethyl acetate 5:1 v/v) showed three major components: **10a**, **1a**, and **3-F** having increasing R_F values. The reaction mixture was cooled in an ice bath and extracted with two 100-ml portions of water. The organic layer was dried and concentrated to a pale-yellow syrup, which was dissolved in anhydrous methanol (100 ml) and a few granules of Na–Pb alloy ("dri-Na", J. T. Baker Chemical Co.) were added. Neutralization of the reaction with Dry Ice, filtration to remove the granules, and evaporation left a semisolid mass, which was triturated with boiling isopropyl alcohol (20 ml). Removal of the solvent gave a syrup that appeared by paper chromatography to be a mixture of **1b** (R_F 0.30), **4** (R_F 0.53), and **10b** (R_F 0.75). Column chromatography (Avicel 250 g, 6×45 cm) of this syrup with butanone–water azeotrope as the eluting solvent separated the mixture into **10b**, 0.70 g, and **4**, 150 mg. Recrystallization from chloroform (5 ml)-petroleum ether (added to the cloudy solution) gave 114 mg (12%) of **4**, m.p. 108.2°, $[\alpha]_D^{24}$ +40° (*c* 0.11, H_2O), R_F 0.53 (lit.[21], m.p. 109–110°, $[\alpha]_D^{21}$ +43°).

Anal. Calc. for $C_7H_{13}FO_5$: C, 42.86; H, 6.68. Found: C, 42.79; H, 6.80.

When this reaction was repeated with undried toluene, or when the tetraethylammonium fluoride was exposed to air for about 5–10 min, the yield of **4** was practically zero.

Methyl 2,3-di-O-benzoyl-4,6-dibromo-4,6-dideoxy-α-D-galactopyranoside (**6**). — Toluene (350 ml), HMPA (8 ml) and lithium bromide (3.4 g) were heated with stirring and then 100 ml of solvent was distilled off under anhydrous conditions. After removal of the heat source and when boiling ceased, **2** (3.5 g) was added to the reaction mixture in one portion, and heating to reflux was resumed for 116 h. The mixture was extracted with three 50-ml portions of water, and the organic layer was dried and concentrated to give a tan liquid (~2.5 g). Dry-column chromatography[13] (180 g Silica Gel G, 4×38 cm) with benzene as the eluting solvent gave from fractions 36–86 (~7 ml fractions) an oily fraction that crystallized slowly on standing. The analysis of this crystalline solid, m.p. 124–131°, 0.78 g (23%), indicated it to be a methyl dibenzoyldibromodideoxyhexoside. Multiple ascent t.l.c. (benzene–petroleum ether 37–47°, 3×) showed a fast (major) and slow (minor) component. Dry-column chromatography (170 g of Silica Gel G, 3×80 cm) of this crystalline solid, with 1 liter each of benzene–hexane 1:1, 3:2, 4:1 v/v, collected from individual fractions from 3 to 7 ml, gave from fractions 150–339, 321 mg of crystalline **6**, Recrystallization from 95% ethanol (8 ml) gave 293 mg of **6**; m.p. 133–135°; $[\alpha]_D^{24}$ $+156°$ (c 0.104, chloroform); R_F 0.71 benzene–ethyl acetate 50:1 v/v; λ_{max} in 95% ethanol 275 (ε 1870), 282 nm (1530); λ_{max}^{KBr} 1725 cm^{-1} (benzoic ester); n.m.r. data 3.46 (OMe); ~3.46 (m, H-6, 2H); 4.2 (t, J ~7 Hz, H-5); 4.84 (m, J <3 Hz, H-4); 5.11 (d, J ~3 Hz, H-1); 5.48–5.51 (m, H-2,3, 2H); 7.2–8.0 δ (m, aryl, 10H).

Anal. Calc. for $C_{21}H_{20}Br_2O_6$: C, 47.75; H, 3.81; Br, 30.25. Found: C, 47.54, H, 4.07, Br, 31.38.

Fractions 340–459 contained **6** but multiple-ascent t.l.c. revealed a trace amount of the slower-migrating component, which was assumed to be **7**.

ACKNOWLEDGMENTS

To Clara E. McGrew, Bonita R. Heaton, and Karen A. Jones for the microchemical analyses and Larry W. Tjarks for the n.m.r. spectra.

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