THE USE OF AMBERLITE IRA-410 FOR PREPARATION OF TERMINAL CHLORODEOXY SUGARS*

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Anion-exchange resin Amberlite IRA-410 was found to be an effective and selective reagent for the nucleophilic displacement of primary tosyloxy (mesyloxy) groups in 3,5-disulfonates of xylofuranose derivatives *I* and *III*, as well as in 3,5,6-trisulfonates and 3,6-ditosyl derivatives of glucofuranose *V*, *VII* and *IX*. In all examined cases only the primary sulfonyloxy groups were replaced with chloride anions, whereupon the corresponding terminal chlorodeoxy derivatives were obtained in good yields.

Deoxy halogeno sugars are among the most important carbohydrate derivatives. They assume key roles in the syntheses of deoxy and anhydro sugars. Also, they serve as useful intermediates in the introduction of heteroatoms and unsaturation into carbohydrate molecules[1]. Although several types of reaction have been used for preparations of halogenated carbohydrates[2], the direct nucleophilic displacement of the corresponding sulfonate esters with halogenides generally have been the most effective[3,4]. Among them, the triflate displacement by tetrabutylammonium halides[4] has been recommended as a method of choice, although it requires use of relatively expensive reagents.

Recently we have reported[5,6] that a readily available and inexpensive anion-exchange resin Amberlite IRA-410 (in chloride[5] as well as in bromide[6] and iodide[6] form) can be used as an effective reagent for the regioselective substitutions of primary 5-O-sulfonate group in 3,5-di-O-methane(toluene)sulfonyl-1,2-O-cyclohexylidene-α-D-xylofuranose derivatives whereupon the corresponding 5-halogeno-5-deoxy derivatives were obtained in high yields. In this paper we want to report the full details of our preliminary communicated results[5] as well as some new results obtained by application

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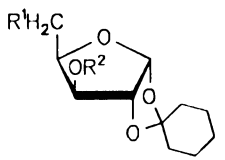
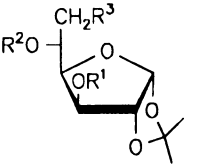
of similar methodology onto selected sulfonate esters of 1,2-O-isopropylidene-α-D-glucofuranose.

Both disulfonates *I* and *III* in xylofuranose series reacted with Amberlite IRA-410 (Cl^-), in boiling N,N-dimethylformamide, whereupon the corresponding 5-chloro-5-deoxy derivatives *II* and *IV* were obtained in high yields (Table I). Under these reaction conditions only the primary sulfonyloxy groups in both *I* and *III* were selectively displaced by chloride anion, whereas the secondary C-3 tosyloxy (mesyloxy) groups remain virtually unchanged. The course of this reaction is in agreement with well known evidence relating to inability of an anionic nucleophile to effect displacement of certain secondary leaving groups attached to a furanose ring[7].





I, R^1 = OTos; R^2 = Tos
II, R^1 = Cl; R^2 = Tos
III, R^1 = OMes; R^2 = Mes
IV, R^1 = Cl; R^2 = Mes

V, $R^1 = R^2$ = Tos; R^3 = OTos
VI, $R^1 = R^2$ = Tos; R^3 = Cl
VII, $R^1 = R^2$ = Mes; R^3 = OMes
VIII, $R^1 = R^2$ = Mes; R^3 = Cl
IX, R^1 = Tos; R^2 = H; R^3 = OTos
X, R^1 = Tos; R^2 = H; R^3 = Cl
XI, R^1 = Tos; R^2 = Bz; R^3 = Cl

Bz = benzoyl
Mes = methanesulfonyl
Tos = *p*-toluenesulfonyl

An attempt to apply the same reaction conditions onto 3,5,6-tri-O-sulfonates *V* and *VII*, in glucofuranose series, resulted in complex reaction mixtures, containing large number of products. Obviously, in both cases *V* and *VII* the vigorous reaction conditions (boiling N,N-dimethylformamide) effected some side competing reactions (eliminations and/or molecular rearrangements). However, by decreasing the reaction temperature an efficient and clean displacement reaction took place. Namely, reactions of both trisulfonates *V* and *VII*, as well as 3,6-ditosylate *IX*, with Amberlite IRA-410 (Cl^-), in a stirred solutions of N,N-dimethylformamide, at 100 °C, gave in high yields the corresponding 6-chloro-6-deoxy derivatives *VI*, *VIII*, and *X*, respectively (Table I).

Under these reaction conditions high regioselectivity has also been achieved. Namely, only the primary sulfonyloxy groups in both *VI* and *VIII* were selectively replaced by chloride anion, while both C-3 and C-5 secondary leaving groups remain unaffected. In the same time, 3,6-ditosylate *IX*, under same reaction conditions gave the corresponding 6-monochloro derivative *X* as the only reaction product in very good yield. The same product *X* has been prepared from ditosylate *IX* by an alternative method, using tetraethylammonium chloride as a source of Cl^- anions. Although the reaction in this case was noticeably faster, whereupon the product *X* was obtained in similar yield as in the experiment with Amberlite IRA-410 (Table I), the former method based on cheaper commercial ion-exchange resin is far more convenient, particularly in large scale preparations of corresponding chloro sugars. Thus prepared product *X* was additionally characterized by conversion into crystalline 5-O-benzoyl derivative *XI*.

As one can see from Table I, methanesulfonate esters *III* and *VI* reacted slightly faster comparing to the corresponding *p*-toluenesulfonate esters *I* and *V*. The difference in reaction rates are particularly significant between mesylate *VII* (requires 12 h to complete the reaction) and tosylate *V* (44 h) in glucofuranose series. Such chemical behaviour was a priori unexpected, because the *p*-toluensulfonyloxy group is known to be somewhat more reactive than the methanesulfonyloxy group in displacement reactions[8], although few exemptions were also described[3]. As it can be further seen, displacement of primary sulfonyloxy groups in glucofuranose series (*V*, *VII*, and *IX*) are also influenced by the nature of neighbouring substituent at C-5. Namely it has been shown that 3,6-ditosylate *IX* reacted with Amberlite IRA-410 considerably faster (7 h to complete the reaction) in respect to both 3,5,6-trisulfonates *V* (44 h) and *VII* (12 h). Obviously that C-5 electron-withdrawing groups in *V* and *VII* destabilize the S_N2 transition state and thus decrease the reactivity of C-6 leaving groups in both trisulfonates *V* and *VII*. On the other hand, it is quite possible that free C-5 hydroxyl group in the

TABLE I
Syntheses of 5-chloro-5-deoxy derivatives with Amberlite IRA-400 (Cl^-) and tetraethylammonium chloride in DMF

Starting compound	Reaction temperature, °C	Reaction time, h	Source of chloride anions	Product yield, %
I	Reflux	15	IRA-410	*II* (70)
III	Reflux	11	IRA-410	*IV* (75)
V	100	44	IRA-410	*VI* (63)
VII	100	12	IRA-410	*VIII* (75)
IX	100	7	IRA-410	*X* (75)
IX	100	1.5	Et_4NCl	*X* (73)

molecule *IX* additionally accelerates the reaction rate, by neighbouring group participation via an 5,6-epoxide intermediate.

The selected ^{13}C NMR data of all synthesized compounds and starting materials are presented in Table II. As one can see, the signals corresponding to primary C atoms in all chlorodeoxy sugars are shifted towards the high-field region, confirming unambiguously that chloro functions were introduced in these positions. It is also interesting to note that chemical shifts of chloromethyl carbon atoms are, more or less, independent of nature of the substituents in β-positions.

In conclusion, the results described here show that ion-exchange resin Amberlite IRA-410 (Cl^-) can be used as an efficient reagent for regioselective displacement of primary sulfonyloxy groups, whereupon the corresponding chlorodeoxy sugars were prepared in good yields. The main advantages of the new method are: (i) The use of cheap and renewable reagent (Amberlite IRA-410), and (ii) simple and fast work-up procedure (removal of the resin by filtration, evaporation of the solvent followed by quick column chromatography and crystallization of the product).

EXPERIMENTAL

Melting points were determined on Buchi SMP 20 apparatus and were not corrected. Optical rotations were measured on automatic polarimeter Polamat A (Zeiss, Jena), at room temperature in chloroform solutions. IR spectra were obtained on Perkin Elmer 457 spectrophotometer and wavenumbers are given in cm^{-1}. NMR spectra were recorded on Bruker WP 200 SY instrument, in deuteriochloroform with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ-scale) and coupling constants (*J*)

TABLE II
^{13}C NMR spectral data (ppm) of the skeletal carbon atoms in compounds *I* – *XI*

Compound	C-1	C-2	C-3	C-4	C-5	C-6
I	104.44	82.63	81.38	78.71	66.00	–
II	104.59	82.63	82.20	79.03	38.84	–
III	104.57	82.85	80.71	76.29	65.57	–
IV	104.74	83.84	81.26	80.47	38.32	–
V	104.49	80.96	82.37	78.13	74.82	67.34
VI	104.51	80.59	82.36	77.41	75.77	43.12
VII	104.98	79.00	82.91	77.70	72.98	68.06
VIII	104.96	79.51	82.95	78.49	73.08	44.48
IX	104.99	82.86	81.44	78.28	71.82	66.39
X	104.99	83.05	81.33	79.19	67.73	47.91
XI	104.87	83.26	80.81	77.63	68.88	43.78

in Hz. Mass spectra were taken on VG-7035 spectrometer (at 70 eV) and positions of fragments are given in *m/e* values. Thin-layer chromatography (TLC) was performed on DC Alufolien Kieselgel 60 F_{254} (Merck). Column chromatography was carried out on Kieselgel 60 (0.063 – 0.2 mm).

General Procedure for Preparation of 5-Chloro-5-deoxy Xylofuranose Derivatives *II* and *IV*

A suspension containing disulfonate ester *I* or *III* (1.85 mmol) and Amberlite IRA-410 (Cl^-) anion resin (15 g of dry resin) in N,N-dimethylformamide (15 ml) was stirred at reflux temperature until the starting material is completely converted into product (TLC, CH_2Cl_2–ethylacetate 9 : 1). The resin was removed by filtration and the solvent distilled off in high vacuum (oil pump). The residue was purified by chromatography on a short column of silica gel (30 g; CH_2Cl_2–ethyl acetate 9 : 1) and recrystallized to give the pure product.

1,2-O-Cyclohexylidene-5-chloro-5-deoxy-3-O-p-toluenesulfonyl-α-D-xylofuranose (II). The ditosylate[9] *I* (1.0 g) afforded 0.52 g (70%) of 5-chloro derivative *II*, m. p. 88 °C (EtOH). $[\alpha]_D$ −79.76° (*c* 0.6). ^{1}H NMR spectrum: 1.3 – 1.5 broad signal, 10 H (cyclohexane ring); 2.4 s, 3 H (CH_3, Tos); 3.4 – 3.57 m, 2 H (H-5 and H-5'); 4.3 m, 1 H (H-4); 4.78 d, 1 H (H-2, *J*(1,2) = 3.7); 4.9 d, 1 H (H-3, *J*(3,4) = 2.9); 5.93 d, 1 H (H-1, *J*(1,2) = 3.7); 7.37 – 7.83 several signals, 4 H (C_6H_4, Tos). ^{13}C NMR spectrum: 21.26 (CH_3, Tos); 23.46, 23.8, 24.78, 35.78, 36.36 (5 × CH_2, cyclohexylidene); 113.5 (O–C–O, cyclohexylidene); 120.11 – 130 (arom. C, Tos). For data of skeletal C atoms see Table II. Mass spectrum: 402 (M^+). For $C_{18}H_{23}ClO_6S$ (402.9) calculated: 53.66% C, 5.75% H, 8.80% Cl, 7.96% S; found: 53.78% C, 5.71% H, 9.0% Cl, 7.83% S.

1,2-O-Cyclohexylidene-5-chloro-5-deoxy-3-O-methanesulfonyl-α-D-xylofuranose (IV). The dimesylate[10] *III* (0.72 g) afforded 0.63 g (75%) of 5-chloro derivative *IV*, m. p. 120 °C (dichloromethane–petroleum ether). $[\alpha]_D$ −51.83° (*c* 0.6). ^{1}H NMR spectrum: 1.53 – 1.69 broad signal, 10 H (cyclohexane ring); 3.13 s, 3 H (Mes); 3.53 – 3.7 m, 2 H (H-5 and H-5'); 4.42 – 4.9 m, 1 H (H-4); 4.61 d, 1 H (H-2, *J*(1,2) = 2.9); 4.84 d, 1 H (H-3, *J*(3,4) = 3.9); 5.94 d, 1 H (H-1, *J*(1,2) = 2.9). ^{13}C NMR spectrum: 23.5, 23.81, 24.77, 36.4, 37.77 (5 × CH_2, cyclohexylidene); 38.32 (Mes); 113.76 (O–C–O, cyclohexylidene). For data of skeletal C atoms see Table II. Mass spectrum: 326 (M^+). For $C_{12}H_{19}ClO_6S$ (326.8) calculated: 44.10% C, 5.86% H, 10.85% Cl, 9.81% S; found: 44.23% C, 6.0% H, 11.0% Cl, 9.61% S.

General Procedure for Preparation of 6-Chloro-6-deoxy Glucofuranose Derivatives *VI* and *VIII*

A suspension containing trisulfonates *V* or *VII* (1.8 mmol) and Amberlite IRA-410 (Cl^-) anion resin (15 g of dry resin) in N,N-dimethylformamide (15 ml) was stirred at 100 °C until the starting compound has disappeared (TLC; CH_2Cl_2–ethyl acetate 19 : 1). After removal of the resin and the solvent the resulting crude mixture was purified on a short column of silica gel (30 g; CH_2Cl_2).

6-Chloro-6-deoxy-1,2-O-isopropylidene-3,5-di-O-p-toluenesulfonyl-α-D-glucofuranose (VI). The tritosylate[11] *V* (1.23 g) afforded 0.62 g (63%) of 6-chloro derivative *VI*, m. p. 136 – 137 °C (EtOH). $[\alpha]_D$ −36.86° (*c* 0.6). ^{1}H NMR spectrum: 1.21 and 1.44 2 × s, 2 × 3 H (2 × CH_3, isopropylidene); 2.45 and 2.48 2 × s, 2 × 3 H (2 × CH_3 from 2 × Tos); 3.66 dd, 1 H (H-6, *J*(6,6') = 13; *J*(6,5) = 3.08); 3.72 dd, 1 H (H-6', *J*(6,6') = 13; *J*(6',5) = 4.62); 4.5 dd, 1 H (H-4, *J*(4,5) = 6.47; *J*(4,3) = 2.77); 4.82 several signals, 2 H (H-2 and H-5); 4.99 d, 1 H (H-3, *J*(3,4) = 2.77); 5.83 d, 1 H (H-1, *J*(1,2) = 3.39); 7.17 – 7.9 several signals, 8 H (2 × Tos). ^{13}C NMR spectrum: 21.68 and 21.74 (2 × CH_3 from 2 × Tos), 26.35 and 26.62 (2 × CH_3, isopropylidene), 113.08 (O–C–O, isopropylidene), 128.04 – 145.78 (arom. C, Tos). For data of skeletal C atoms see Table II. For $C_{23}H_{27}ClO_9S_2$ (547.0) calculated: 50.50% C, 4.97% H, 6.48% Cl, 11.72% S; found 50.68% C, 5.08% H, 6.78% Cl, 12.0% S.

6-Chloro-6-deoxy-1,2-O-isopropylidene-3,5-di-O-methanesulfonyl-α-D-glucofuranose (VIII). The trimesylate[12] *VII* (0.82 g) afforded 0.53 g (75%) of 6-chloro derivative *VIII*, m. p. 125 – 126 °C (CH_2Cl_2–petroleum ether). $[\alpha]_D$ − 31.6° (*c* 1.4). ^{1}H NMR spectrum: 1.33 and 1.52 2 × s, 2 × 3 H (2 × CH_3, isopropylidene); 3.19 s, 6 H (2 Mes); 3.85 dd, 1 H (H-6, *J*(5,6) = 3.5; *J*(6,6') = 12.9); 4.11 dd, 1 H (H-6', *J*(5,6') = 2.4;

$J(6,6')$ = 12.9); 4.94 – 5.05 several signals, 2 H (H-2 and H-5); 5.11 d, 1 H (H-3, $J(3,4)$ = 2.6); 5.96 d, 1 H (H-1, $J(1,2)$ = 3.5). ^{13}C NMR spectrum: 26.41 and 26.75 (2 × CH_3, isopropylidene), 38.6 and 39.22 (2 × CH_3SO_2), 113.32 (O–C–O, isopropylidene). For data of skeletal C atoms see Table II. For $C_{11}H_{19}ClO_6S_2$ (394.8) calculated: 33.46% C, 4.81% H; found 33.23% C, 4.72% H.

6-Chloro-6-deoxy-1,2-O-isopropylidene-3-O-*p*-toluenesulfonyl-α-D-glucofuranose (*X*)

A) A suspension containing ditosylate[13] *IX* (0.93 g; 1.8 mmol) and Amberlite IRA-410 (Cl^-) anion resin (15 g) in N,N-dimethylformamide (15 ml) was stirred at 100 °C for 7 h. After removal of the resin and the solvent, the resulting crude mixture was purified on a column of silica gel (30 g; cyclohexane–acetone 4 : 1), to give the pure product *X* as a colourless oil (0.53 g; 75%), $[\alpha]_D$ −14.14° (*c* 1.92). IR spectrum (film): 3 520 (OH). ^{1}H NMR spectrum: 1.28 and 1.47 2 × s, 2 × 3 H (2 × CH_3, isopropylidene); 2.47 s, 3 H (CH_3, Tos); 2.59 d, 1 H (OH, J(5,OH) = 5.7); 3.65 dd, 1 H (H-6, $J(6,6')$ = 11.2; $J(6,5)$ = 5.8); 3.85 dd, 1 H (H-6', $J(6',6)$ = 11.2; $J(6',5)$ = 2.5); 3.96 dddd, 1 H (H-5, $J(5,4)$ = 9; $J(5,6)$ = 5.8; J(5,OH) = 5.7; $J(5,6')$ =2.5); 4.2 dd, 1 H (H-4, $J(4,5)$ = 9; $J(4,3)$ = 2.6); 4.6 d, 1 H (H-2, $J(2,1)$ = 3.5); 4.98 d, 1 H (H-3, $J(3,4)$ = 2.6); 5.87 d, 1 H (H-1, $J(1,2)$ = 3.5); 7.36 – 7.90 several signals, 4 H (C_6H_4, Tos). ^{13}C NMR spectrum: 21.64 (CH_3, Tos), 26.35 and 26.65 (2 × CH_3, isopropylidene), 112.88 (O–C–O, isopropylidene), 128.06 – 145.67 (arom. C, Tos). For skeletal C atoms see Table II. Mass spectrum: 395 (M^+ + 2), 393 (M^+), 378 (M^+ – CH_3). For $C_{16}H_{21}ClO_7S$ (392.9) calculated: 48.92% C, 5.39% H, 9.02% Cl, 8.15% S; found: 48.77% C, 5.24% H, 9.02% Cl, 7.99% S.

B) A solution of compound *IX* (0.66 g; 1.25 mmol) and tetraethylammonium chloride (0.31 g; 1.87 mmol) in dry N,N-dimethylformamide (5 ml) was stirred at 100 °C for 1.5 h. After removal of the solvent the crude residue was dissolved in CH_2Cl_2 (15 ml). The solution was washed with water (3 × 30 ml), dried (Na_2SO_4) and evaporated to left a crude *X* as a brown oil. After chromatographic purification on a column of silica gel (18 g; cyclohexane–acetone 4 : 1) the pure product *X* was obtained in a form of colourless syrup (0.36 g; 73%). Thus prepared compound *X* was identical with product obtained according to procedure *A*.

5-O-Benzoyl-6-chloro-6-deoxy-1,2-O-isopropylidene-3-O-*p*-toluenesulfonyl-α-D-glucofuranose (*XI*)

A solution of compound *X* (0.03 g; 0.08 mmol) and benzoyl chloride (0.02 g; 0.14 mmol) in dry pyridine (1 ml) was kept at room temperature for 24 h. The reaction mixture was poured into diluted hydrochloric acid (HCl/H_2O = 1 : 4; 5 ml) and extracted with dichloromethane. The extract was washed with saturated $NaHCO_3$ solution and water, dried (Na_2SO_4) and evaporated, to left a white solid. The crude product *XI* was recrystallized from cyclohexane to give the pure *XI* (0.03 g; 79%) as colourless needles, m. p. 127 °C. IR spectrum (KBr): 1 720 (C=O, Bz). ^{1}H NMR spectrum: 1.36 and 1.56 2 s, 2 × 3 H (2 × CH_3, isopropylidene); 2.15 s, 3 H (CH_3, Tos); 3.88 dd, 1 H (H-6', $J(6',6)$ = 12.5; $J(6',5)$ = 2.75); 4.06 dd, 1 H (H-6, $J(6,6')$ = 12.5; $J(6,5)$ = 2.75); 4.73 dd, 1 H (H-4, $J(4,5)$ = 9.25; $J(4,3)$ = 2.75); 4.99 several signals, 2 H (H-2 and H-3), 5.24 dt, 1 H (H-5, $J(5,4)$ = 9.25; $J(5,6)$ = $J(5,6')$ = 2.75); 5.98 d, 1 H ($J(1,2)$ = 3.5); 7.0 – 7.9 several signals, 9 H (arom. H, Bz and Tos). ^{13}C NMR spectrum: 21.5 (CH_3, Tos), 26.47 and 26.81 (2 × CH_3, isopropylidene), 113.12 (O–C–O, isopropylidene), 127.84 – 145.33 (arom. C, Bz and Tos), 164.69 (C=O). Mass spectrum: 481 (M^+ – CH_3). For $C_{23}H_{25}ClO_8S$ (497.72) calculated: 55.59% C, 5.07% H, 7.13% Cl, 6.45% S; found: 55.16% C, 5.1% H, 6.89% Cl, 6.21% S.

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