Reaction of Carbohydrates with Methylsulfonyl Chloride in *N,N*-Dimethylformamide. Preparation of Some Methyl 6-Chloro-6-deoxyglycosides[1]

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Reaction of hexopyranosides with methylsulfonyl chloride in *N,N*-dimethylformamide causes selective replacement of the primary hydroxyl groups by chlorine. The resulting 6-chloro-6-deoxyhexopyranosides are reduced to 6-deoxyhexopyranosides by lithium aluminum hydride in tetrahydrofuran. These reactions provide an improvement over current syntheses of 6-chloro-6-deoxyhexopyranosides and 6-deoxyhexopyranosides in the yield and number of steps involved.

Selective reactions of hydroxyl groups have led to useful intermediates in carbohydrate chemistry. In the case of carbohydrates containing primary hydroxyl groups, reaction with triphenylmethyl chloride in pyridine to form trityl ethers has been widely used because of the high yield and selectivity of the reaction and the ease of subsequent regeneration of the hydroxyl group with acid.[4] Recent studies[5,6] in our laboratories have been concerned with selective methylsulfonylation of methyl hexopyranosides in anhydrous pyridine and in mixtures of pyridine and triethylamine and of pyridine and *N,N*-dimethylformamide (DMF); these variations in solvent do not alter significantly the selectivity of the mesylation reaction. The present paper describes the results obtained when some methyl hexopyranosides were treated with methylsulfonyl chloride in DMF.

Initially we used the conditions described by Chalk, *et al.*,[6] that is, 2 equiv of methylsulfonyl chloride was added slowly to a solution of methyl α-D-glucopyranoside (**1**) in DMF at −20 to −40°. Thin layer chromatograms of the reaction mixture after 16 hr showed the presence of a product with mobility the same as that of methyl 6-chloro-6-deoxy-α-D-glucopyranoside (**2**) but different from that of methyl 6-*O*-mesyl-α-D-glucopyranoside (**3**), fast moving materials which gave a positive test for ester with ferric hydroxamate,[7] and a large amount of compound **1**. The fast moving materials were identified as *O*-formate esters of compounds **1** and **2** from consideration of their nmr spectra and the nature of the deesterification products. These esters, which partially decomposed during silica gel chromatography or on storage at room temperature, were generally deesterified with sodium methoxide prior to column chromatography. We avoided the use of ketones as eluents during this work as we found that the use of methyl ethyl ketone as eluent in column chromatography on Brinkmann silica gel leads to acetal formation between the ketone and unchanged **1**.

Fractionation of the deesterified reaction mixture on silica gel with ethyl acetate–ethanol–water (45:5:3) as the eluent gave chromatographically pure **2** in 64% yield, which crystallized on removal of the solvent. Recrystallization from 1-propanol gave material having melting point and specific rotation identical with those reported by Helferich, *et al.*[8] Elemental analysis values agreed with those expected for $C_7H_{13}O_5Cl$ and the absence of sulfur was shown. The nmr spectrum in D_2O showed the presence of 10 protons and the absence of an *O*-mesyl group; the infrared spectrum showed a strong band at 13.3 μ (>CCl) but no bands at 7.3 and 8.5 μ (*O*-mesyl).[9] Edington[10] reported the formation of formate esters in quantitative yield during tosylation of bis-2-hydroxyethyl terephthalate in DMF for 15 min at −5°, whereas at 65° for 4 hr or 100° for 15 min bis-2-chloroethyl terephthalate was obtained in 94% yield. We therefore tried raising the reaction temperature in our experiments; at 30° little change in the yield of compound **2** was observed but at 100° the yield was almost quantitative (Table I).

TABLE I

YIELDS OF METHYL 6-CHLORO-6-DEOXY-D-GLYCOPYRANOSIDES

Starting glycoside	Mesyl chloride, equiv	Temp, °C	Isolated yield of 6-chloro-6-deoxy product, %
Methyl α-D-glucopyranoside	2	−25	64
	2	30	59
	2	65	97
Methyl β-D-glucopyranoside	2	−25	42
	2	65	38
	10	−25	40
	10	65	91
Methyl α-D-mannopyranoside	10	65	86

Hess and Pfleger[11] reported the replacement of a primary tosyloxy group by chlorine during the tosylation of starch in pyridine above 30°. Similarly, bis-2-toluene-*p*-sulfonyloxyethyl terephthalate was converted into bis-2-chloroethyl terephthalate by treatment with pyridine and *p*-tolylsulfonyl chloride at 65°.[10] When methyl 6-*O*-mesyl-α-D-glucopyranoside (**3**) was treated with methylsulfonyl chloride and DMF at −25°, conditions which led to the conversion of **1** into **2** in 64% yield, unchanged **3** was recovered quantitatively demonstrating that **3** is not an intermediate in the conversion of **1** into **2**.

Albright and coworkers[12] have used *p*-tolylsulfonyl chloride in DMF with testosterone to give testosterone

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O-formate in 79% yield. These workers proposed a mechanism based on nucleophilic attack by alcohol R_3C^*OH on the iminium salt $(Me_2N^+{=}CHOSO_2C_6H_4\text{-}Me)Cl^-$, derived from *p*-tolylsulfonyl chloride and DMF, to give an intermediate $Me_2N^+{=}CHOC^*R_3$ which is hydrolyzed to an *O*-formate. Edington[10] proposed the same mechanism to explain the production of bis-2-formyloxyethyl terephthalate. Attack by chloride ion on the above intermediate was postulated[12] to explain the formation in high yield of *p*-nitrobenzyl chloride from *p*-nitrobenzyl alcohol and of picryl chloride from picric acid. This mechanism appears to us to be the most likely explanation of the formation of bis-2-chloroethyl terephthalate from the corresponding alcohol in DMF–tosyl chloride, of the introduction of chlorine at the C-21 position of the 11α-acetoxy and 19-acetoxy derivatives of 17α, 21-dihydroxy-4-pregnene-3,20-dione[13] by DMF–tosyl chloride, and of our observations with glycosides.

As conductivity[14] and nmr[15] studies have shown that the concentration of the iminium salt is low, the rate of formation of this salt may be the rate-determining step. We attempted without success to improve the yield of compound **2** by reaction of the glycoside **1** with methylsulfonyl chloride in DMF in the presence of 1 equiv of lithium chloride (based on the amount of glucoside) at −25°. While deionizing the product of this reaction on a column of Rexyn 300 mixed bed resin we observed that unchanged **1** emerged before the product **2**. Following this observation we have developed a separation procedure[16] for mixtures of **1**, **2**, and methyl 6-deoxy-α-D-glucopyranoside (and for the β anomers) using anion-exchange resin with 75% aqueous 1-propanol as eluent. Mattisson and Samuelson have described a similar procedure.[17]

When methyl β-D-glucopyranoside was treated with 2 equiv of methylsulfonyl chloride in DMF at −25 or at 65°, methyl 6-chloro-6-deoxy-β-D-glucopyranoside (**4**)[18] was obtained in about 40% yield (Table I). Using 10 equiv of methylsulfonyl chloride at −25° the yield of **4** was again moderate, but at 65° the yield improved to 91%.

Treatment of methyl α-D-mannopyranoside with 10 equiv of methylsulfonyl chloride in DMF at 65° gave crystalline methyl 6-chloro-6-deoxy-α-D-mannopyranoside, known previously[19] only as a syrup, in 86% yield.

The use of methylsulfonyl chloride in DMF provides a selective method for the replacement of a primary hydroxyl group by chlorine; only trace amounts of compounds in which secondary hydroxyl groups had been substituted were encountered, and in the case of methyl α-D-xylopyranoside 99% of unchanged glycoside was recovered from the reaction. We have used the method successfully with other carbohydrate materials including disaccharides, cyclodextrins, and nucleosides; we will report these results later. The use of other compounds containing both sulfur and halogen, *e.g.*, *p*-tolylsulfonyl chloride,[12] sulfuryl chloride,[20] thionyl chloride,[21] or sulfur monochloride,[22] in place of methylsulfonyl chloride led to inferior yields of the chloro sugars. We have successfully employed N,N-dimethylacetamide in place of DMF.

Attempts to prepare methyl 6-deoxy-6-fluoro-α-D-glucopyranoside by this procedure using methylsulfonyl fluoride have so far been unsuccessful; the use of methanesulfonic anhydride in the hope of preparing 6-*O*-methylsulfonates led to the formation of *O*-formates.

Methyl 6-chloro-6-deoxyhexopyranosides can be reduced to the corresponding 6-deoxy sugars by lithium aluminum hydride in boiling tetrahydrofuran. For example, **2** is reduced to methyl 6-deoxy-α-D-glucopyranoside[23] in 87% yield; together with the methylsulfonyl chloride–DMF reaction this reduction provides a convenient preparation for 6-deoxyglycosides, superior to current methods[24,25] in both yield and number of steps involved.

Having achieved selective reaction at the primary hydroxyl group, in order for the chlorine atom that was introduced to be considered a good blocking substituent, it was necessary to regenerate the hydroxyl group in high yield. A convenient method is to regenerate the primary hydroxyl group from **2** via the 6-*O*-benzoate ester[26] by benzoate exchange[27] in DMF.

The chlorodeoxy- and deoxyglycosides described in this paper have been examined as substrates or inhibitors of glycosidases.[28]

Experimental Section[29]

General Procedure.—Methylsulfonyl chloride (2 or 10 equiv based on the amount of glycoside) was added dropwise to a stirred solution of the glycoside in anhydrous DMF (0.1 g/ml) maintained at the desired reaction temperature. After 16 hr at this temperature the mixture was concentrated to a syrup which was then dissolved in methanol and treated with sodium methoxide to destroy *O*-formate esters. The solution was concentrated and the product was chromatographed on silica gel. Elution with solvent 2 gave the methyl 6-chloro-6-deoxyglycoside and elution with ethyl acetate–methanol (9:1) gave unchanged methyl glycoside. The course of the fractionation was followed by tlc using solvents 1 or 2. The methyl 6-chloro-6-deoxyglycosides crystallized on removal of the solvent.

In some experiments with methyl α- and β-D-glucopyranosides the effect of the presence of dry lithium chloride (0.25 g/g of glycoside) in the reaction mixture was examined.

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(29) Solutions were concentrated under reduced pressure. Melting points were determined with a Thomas–Hoover capillary melting point apparatus and optical rotations were measured using an ETL-NPL automatic polarimeter. Nmr spectra were recorded on a Varian Model A-60 spectrometer. Ascending thin layer chromatography (tlc) was performed on silica gel GF_{254}; solvent 1 refers to benzene–chloroform–isopropyl alcohol (3:3:1) and solvent 2 is composed of ethyl acetate–ethanol–water (45:5:3). For the detection of spots, the chromatoplates were sprayed successively with a 1% solution of α-naphthol in ethanol and with 10% sulfuric acid and were then heated. Silica gel column chromatography was performed on Brinkmann silica gel (0.05–0.20 mm) using 100 g of silica gel for 1 g of sugar mixture. The microanalyses were performed by Mr. C. DiPietro and the nmr spectra by Mr. F. H. Bissett.

Methyl 6-Chloro-6-deoxy-α-D-glucopyranoside.[8]—Treatment of methyl α-D-glucopyranoside (1.2 g) in DMF with methylsulfonyl chloride (1.06 ml, 2 equiv) at −25, 30, or 65°, as described above, gave methyl 6-chloro-6-deoxy-α-D-glucopyranoside with mp 113–114° and $[\alpha]^{30}D$ +139° (*c* 2.4, water) after recrystallization from 1-propanol. Constants previously reported[8] are mp 110–112° and $[\alpha]D$ +139.7° (*c* 2.5, water).

Anal. Calcd for $C_7H_{13}O_5Cl$: C, 39.52; H, 6.16; Cl, 16.69. Found: C, 39.23; H, 6.15; Cl, 16.82.

The yields of crystalline product under various reaction conditions are shown in Table I.

Methyl 6-Chloro-6-deoxy-β-D-glucopyranoside.[18]—Treatment of methyl β-D-glucopyranoside (1.2 g) in DMF with methylsulfonyl chloride (2 or 10 equiv) at −25 or 65° gave methyl 6-chloro-6-deoxy-β-D-glucopyranoside with mp 157–159° and $[\alpha]^{30}D$ −49° (*c* 1.0, water) after recrystallization from 1-propanol, in good agreement with values of mp 156–157°, $[\alpha]D$ −48.7° (*c* 2.5, water) previously reported.[18]

Anal. Calcd for $C_7H_{13}O_5Cl$: C, 39.52; H, 6.16; Cl, 16.69. Found: C, 39.34; H, 6.15; Cl, 16.72.

The yields of crystalline product under various reaction conditions are shown in Table I.

Methyl 6-Chloro-6-deoxy-α-D-mannopyranoside.[19]—Methyl α-D-mannopyranoside (1.2 g) was treated in DMF at 65° for 16 hr with methylsulfonyl chloride (10 equiv) and the reaction mixture was worked up to yield methyl 6-chloro-6-deoxy-α-D-mannopyranoside (1.124 g, 86% yield) with mp 75° and $[\alpha]^{30}D$ +60° (*c* 1.0, water) after recrystallization from 1-propanol. Jennings and Jones[19] report $[\alpha]D$ +59° (*c* 1.0, water).

Anal. Calcd for $C_7H_{13}O_5Cl$: C, 39.52; H, 6.16; Cl, 16.69. Found: C, 39.60; H, 6.18; Cl, 16.84.

The crystalline methyl 6-chloro-6-deoxy-α-D-mannopyranoside (0.5 g) was dissolved in 1 *N* sodium hydroxide (5 ml), kept for 10 hr at 30°, then deionized and concentrated to give methyl 3,6-anhydro-α-D-mannopyranoside (0.37 g, 93% yield) with mp 129° and $[\alpha]^{30}D$ +96° (*c* 3.0, water) after recrystallization from ethanol–benzene in good agreement with values reported previously.[30]

Anal. Calcd for $C_7H_{12}O_5$: C, 47.73; H, 6.82. Found: C, 47.86; H, 6.87.

Reaction with Methyl α-D-Xylopyranoside.—When methyl α-D-xylopyranoside (1.02 g) was treated in DMF at 65° for 16 hr with methylsulfonyl chloride (10 equiv), unchanged starting material (1.01 g, 99%) was recovered.

Methyl 6-Deoxy-α-D-glucopyranoside.[8,23]—Methyl 6-chloro-6-deoxy-α-D-glucopyranoside (200 mg) was treated for 16 hr with lithium aluminum hydride (100 mg) in boiling tetrahydrofuran (15 ml). Excess lithium aluminum hydride was decomposed by the cautious addition of ethyl acetate and the mixture was filtered. The filtrate was concentrated to dryness and the residue deionized with Amberlite MB-3 to give methyl 6-deoxy-α-D-glucopyranoside (145 mg, 87% yield) with mp 99° and $[\alpha]^{30}D$ +158° (*c* 1.0, water) after recrystallization from ethyl acetate.

Anal. Calcd for $C_7H_{14}O_5$: C, 47.19; H, 7.87. Found: C, 47.06; H, 7.80.

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Methyl 6-Deoxy-β-D-glucopyranoside.—Methyl 6-chloro-6-deoxy-β-D-glucopyranoside (1.0 g) was treated for 24 hr with lithium aluminum hydride (500 mg) in boiling tetrahydrofuran (50 ml). After 24 hr additional lithium aluminum hydride (500 mg) was added and the reaction was continued for a further 24 hr. Excess lithium aluminum hydride was decomposed by cautious addition of moist tetrahydrofuran to the cooled mixture. Insoluble material was removed by filtration and the filtrate was concentrated to dryness. The product was worked up by silica gel chromatography to give methyl 6-deoxy-β-D-glucopyranoside (800 mg, 96% yield) with mp 130–131° and $[\alpha]^{30}D$ −42° (*c* 2.0, water) after recrystallization from ethyl acetate.

Anal. Calcd for $C_7H_{14}O_5$: C, 47.19; H, 7.87. Found: C, 47.13; H, 7.88.

Methyl 6-Deoxy-α-D-mannopyranoside.[25]—Methyl 6-chloro-6-deoxy-α-D-mannopyranoside (625 mg) was reduced with lithium aluminum hydride in boiling tetrahydrofuran, as described for the preparation of methyl 6-deoxy-β-D-glucopyranoside, to provide syrupy methyl 6-deoxy-α-D-mannopyranoside (435 mg, 83% yield) with $[\alpha]^{30}D$ +61° (*c* 1.0, water) in agreement with the value reported previously.[25]

Anal. Calcd for $C_7H_{14}O_5$: C, 47.19; H, 7.87. Found: C, 47.09; H, 7.84.

Methyl 6-deoxy-α-D-mannopyranoside (360 mg) was treated for 16 hr in pyridine (5 ml) with benzoyl chloride (1 ml) and worked up in the usual manner[25] to give methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-α-D-mannopyranoside (890 mg, 90% yield) with mp 133° and $[\alpha]^{30}D$ −176° (*c* 0.7 chloroform) after recrystallization from methanol in agreement with values reported previously.[25]

Methyl 6-*O*-Benzoyl-α-D-glucopyranoside.[26]—Methyl 6-chloro-6-deoxy-α-D-glucopyranoside (343 mg) was treated for 16 hr with sodium benzoate (1 g) in boiling DMF (30 ml); then the mixture was concentrated to dryness. The residue was dissolved in water and the solution was passed through a column of Amberlite IR-120 (H^+ form). The effluent was extracted with ether to remove benzoic acid and the aqueous solution was concentrated to a chromatographically pure syrup which gave crystalline methyl 6-*O*-benzoyl-α-D-glucopyranoside (357 mg, 74% yield) with mp 131° and $[\alpha]D$ +108° (*c* 1.2, water) after recrystallization from ethanol, identical with an authentic sample.[26]

Anal. Calcd for $C_{14}H_{18}O_7$: C, 53.85; H, 5.77. Found: C, 53.81; H, 5.75.

Registry No.—Methylsulfonyl chloride, 124-63-0; *N*,*N*-dimethylformamide, 68-12-2; methyl 6-chloro-6-deoxy-α-D-glucopyranoside, 4144-87-0; methyl 6-chloro-6-deoxy-β-D-glucopyranoside, 4990-84-5; methyl 6-chloro-6-deoxy-α-D-mannopyranoxide, 4990-80-1; methyl 3,6-anhydro-α-D-mannopyranoside, 15814-56-9; methyl 6-deoxy-α-D-glucopyranoside, 5155-43-1; methyl 6-deoxy-β-D-glucopyranoside, 6340-52-9; methyl 6-deoxy-α-D-mannopyranoside, 15814-59-2; methyl 6-*O*-benzyl-α-D-glucopyranoside, 4338-28-7.