Novel Reagent System for converting a Hydroxy-group into an Iodo-group in Carbohydrates with Inversion of Configuration. Part 3 †

By **Per J. Garegg**, **Rolf Johansson**, **Carmen Ortega**, and **Bertil Samuelsson**, Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm, S-106 91 Stockholm, Sweden

The use of mixed solvents, toluene and acetonitrile in a ratio of 2 : 1, in the iodine (or tri-iodoimidazole)–imidazole–triphenylphosphine halogenation system allows certain transformations of hydroxy-groups into deoxyiodo-groups which were difficult to achieve in the original system using toluene alone.‡

HALOGEN–IMIDAZOLE–TRIPHENYLPHOSPHINE systems are useful reagents in synthetic carbohydrate chemistry.[1-6] Thus, they allow the one-step conversion of vicinal diols into olefins,[2-4] and displacement with inversion of configuration of single free hydroxy-groups by bromine or iodine in otherwise protected carbohydrates. They also allow selective displacement with iodine of primary hydroxy-groups in the presence of free secondary ones as well as some unusual selective displacements of one primary and one secondary hydroxy-group by bromine in unprotected hexopyranosides.[6]

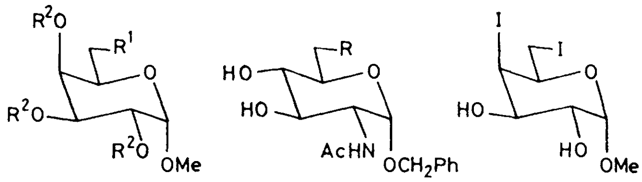
The one-step olefin synthesis [2,3] has been repeated using iodoform [7] instead of iodine or tri-iodoimidazole.

In all these reactions,[1-7] toluene has been used as solvent. The reactant carbohydrate is often insoluble in toluene and the reactions appear to occur in the imidazole–phosphonium phase. In the present work, we describe the use of a more polar solvent, toluene–acetonitrile in a ratio of 2 : 1. This promotes certain substitution reactions in unprotected hexopyranosides which were not achieved using toluene as the single solvent. Thus, in toluene alone, the formation of methyl 6-deoxy-6-iodo-α-D-galactopyranoside (3) from methyl α-D-galactopyranoside (1) was accompanied by the formation of methyl 3,6-anhydro-α-D-galactopyranoside.[8] In attempted displacement of 6-OH in methyl α-D-galactopyranoside (1) with bromine using toluene as solvent no distinct product was obtained. Using toluene–acetonitrile (2 : 1) the corresponding reaction occurred and the 3,6-anhydrosugar was the sole product. Also, the reaction of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside (2) in toluene with iodine or tri-iodoimidazole–imidazole–triphenylphosphine gave complicated reaction mixtures.

Hanessian and his co-workers have described the selective substitution by bromine of 6-OH in 55% yield in compound (1), using *N*-bromosuccinimide and triphenylphosphine.[9] Bundle and Josephson have reported selective substitution by chlorine of 6-OH in methyl 2-deoxy-2-phthalimido-β-D-glucopyranoside using sulphuryl chloride in pyridine.[10]

In the present work, the transformation of compound (1) into (3) and (2) into (4) in toluene–acetonitrile requires reagents in excess and higher reaction temperatures than those used previously in selective substitutions by iodine,[1,4,5] indicating the low reactivity at the primary positions of compounds (1) and (3). The yields of compounds (3) and (4) were 63 and 70% respectively.

Methyl α-D-glucopyranoside upon reaction with iodine, imidazole and triphenylphosphine in toluene–acetonitrile (2 : 1) affords methyl 4,6-dideoxy-4,6-di-iodo-α-D-galactopyranoside (5) in 70% yield. The substitution



(1) R^1 = OH R^2 = H (2) R = OH (5)
(3) R^1 = I R^2 = Ac (4) R = I

pattern in compound (5) was confirmed by acetylation followed by hydrogenation with 10% palladium on carbon to yield derivatives whose structures were assigned by n.m.r. Interestingly, this regioselectivity differs from that in substitutions by bromine using toluene as solvent,[6] which afforded methyl 3,6-dibromo-3,6-dideoxy-α-D-allopyranoside. The corresponding reaction was repeated in the present work in toluene–acetonitrile (2 : 1); the same 3,6-dibromo-dideoxy-product as that obtained previously [6] was obtained.

The selectivity obtained in the substitutions by iodine in the present work, however, is similar to that obtained by Jennings and Jones [11] for the chlorination using sulphuryl chloride in pyridine of methyl α-D-glucopyranoside which gave a 19% yield of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside, and to that obtained by Edwards [12] and his co-workers who effected the same transformation in an 8% yield using the methanesulphonyl chloride–*N*,*N*-dimethylformamide reagent.

† Part 2, ref. 1.
‡ In Part 2, the solvent used for the iodinations was toluene. Regrettably the solvent was erroneously omitted in the descriptions of the syntheses of two compounds, namely (10) (method A) and (11) (method B) in that paper.

EXPERIMENTAL

General Methods.—These were the same as those published before.[1]

2,4,5-Tri-iodoimidazole [1,3,13] (*Modified Procedure*).—Sodium hydroxide (16.0 g, 0.4 mol) in water (200 ml) was added, with stirring, during the course of 1 h to iodine (76.1 g, 0.3 mol) and imidazole (6.81 g, 0.1 mol) in water (2 l) and light petroleum (b.p. 60—71 °C) (1.7 l). The mixture was stirred at room temperature overnight after which the pH of the aqueous phase was lowered to *ca.* 5 by the gradual addition of concentrated hydrochloric acid. The precipitate was filtered off, washed with water, and dissolved in hot methanol (350 ml) containing imidazole (4.5 g). The mixture was refluxed until an almost clear solution was obtained. The hot solution was filtered and the filtrate left in a deep freeze overnight. After the crystals had been filtered off, the mother liquor was concentrated to *ca.* 100 ml to obtain a further crop of crystals. Compact yellow crystals (42.3 g) were obtained.

Methyl 2,3,4-Tri-O-acetyl-6-deoxy-6-iodo-α-D-galactopyranoside [14] (3).—Iodine (2.72 g, 10.7 mmol) was added in portions to a mixture of methyl α-D-galactopyranoside (1.00 g, 5.14 mmol, finely powdered), triphenylphosphine (3.02 g, 11.5 mmol), and imidazole (1.59 g, 23.3 mmol) in toluene–acetonitrile (2 : 1, 60 ml) stirred at 90 °C. After 2 h the mixture was cooled to room temperature. Water (50 ml) and toluene (20 ml) were added to the mixture which was then shaken vigorously and transferred to a separating funnel. The organic phase was extracted with water until only triphenylphosphine and triphenylphosphine oxide remained in the organic phase (t.l.c., ethyl acetate–methanol–water 85 : 10 : 5). The combined aqueous phase was washed with a small amount of toluene and then concentrated. The residue was acetylated with acetic anhydride and pyridine at room temperature. When the acetylation was complete (t.l.c.), the reaction mixture was concentrated and the residue dissolved in toluene. The toluene solution was extracted with water in order to remove imidazole impurities, dried, and concentrated. The product, which did not crystallize, was purified by chromatography on a short silica-gel column (toluene–ethyl acetate 1 : 1) to yield compound (3) (1.41 g, 63%), $[\alpha]_{578}^{22}$ +143° (*c*, 1, chloroform) [lit.,[14] $[\alpha]_{578}^{22}$ +146° (*c*, 1, chloroform)], $\delta(^{13}C)$ (25 MHz, $CDCl_3$) 0.75 (C-6), 20.6 and 20.8 (3 × $COCH_3$), 55.8 (OCH_3), 67.5, 67.8, 69.2, and 69.5 (C-2, C-3, C-4, C-5), 97.2 (C-1), and 169.7, 170.1, and 170.2 (3 × $COCH_3$).

Benzyl 2-Acetamido-2,6-dideoxy-6-iodo-α-D-glucopyranoside (4).—A mixture of triphenylphosphine (1.33 g, 5.07 mmol) and tri-iodoimidazole (1.10 g, 2.47 mmol) was added portionwise during the course of 6 h to a stirred solution of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside (400 mg, 1.28 mmol) in toluene–acetonitrile (2 : 1; 30 ml) at 90 °C. The reaction was complete after 8 h after which the mixture was cooled, concentrated, and then separated on a silica-gel column (ethyl acetate–methanol 9 : 1) to yield compound (4) (380 mg, 70%), m.p. 190—192 °C (crystallized from acetone), $[\alpha]_D^{22}$ +155° (*c*, 1.1, methanol), $\delta(^{13}C)$ [25 MHz, $(CD_3)_2SO$] 8.6 (C-6), 23.1 ($COCH_3$), 55.7 (C-2), 70.4, 72.2, 73.1, and 76.5 (C-3, C-4, C-5, CH_2Ph), 97.8 (C-1), and 173.2 ($COCH_3$) (Found: C, 42.7; H, 4.62; I, 30.2; N, 3.28. $C_{15}H_{20}INO_5$ requires C, 42.8; H, 4.79; I, 30.2; N, 3.33%).

Methyl 4,6-Dideoxy-4,6-di-iodo-α-D-galactopyranoside (5).—Methyl α-D-glucopyranoside (5.00 g, 25.7 mmol), triphenylphosphine (16.8 g, 64.0 mmol), imidazole (4.3 g, 63.6 mmol), and iodine (13.0 g, 51.2 mmol) were added in that order to stirred toluene–acetonitrile (2 : 1, 250 ml). After the mixture had been stirred at 70 ± 3 °C for 1 h more triphenylphosphine (16.8 g, 64.0 mmol), imidazole (4.3 g, 63.6 mmol), and iodine (13.0 g, 51.2 mmol) were added and the reaction mixture was stirred at 70 ± 3 °C for 3 h. The mixture was filtered while warm and the filtrate was concentrated to *ca.* 50 ml. The gummy product was washed with 50-ml portions of cold toluene and then with cold water (50 ml). The supernatant liquids were carefully decanted off. This procedure was repeated six times to remove most of the imidazole, salts, triphenylphosphine, and triphenylphosphine oxide. The resulting gum was dissolved in dichloromethane, dried ($MgSO_4$), filtered, concentrated, and purified by chromatography on a short silica-gel column starting with chloroform–methanol (19 : 1) and finishing with chloroform–methanol (9 : 1) as eluants to yield compound (5) (7.50 g, 70%), $[\alpha]_D^{22}$ +102.5° (*c*, 1, chloroform) (Found: C, 20.2; H, 2.83; I, 61.2. $C_7H_{12}I_2O_4$ requires C, 20.3; H, 2.92; I, 61.3%).

Acetylation of compound (5) with acetic anhydride and pyridine (1 : 1) at room temperature and the usual work-up afforded *methyl 2,3-di-O-acetyl-4,6-dideoxy-4,6-di-iodo-α-D-galactopyranoside*, $\delta(^1H)$ (100 MHz, $CDCl_3$) 2.08, 2.10 (2 s, each 3 H, 2 $COCH_3$), 3.14 (dd, 2 H, 6-H), 3.34 (dd, 1 H, 5-H), 3.47 (s, 3 H, OCH_3), 4.54 (dd, 1 H, 3-H), 4.86 (dd, 1 H, 4-H), 4.94 (d, 1 H, 1-H), and 5.14 (dd, 1 H, 2-H) ($J_{1,2}$ 3.7 Hz, $J_{2,3}$ 10.3 Hz, $J_{3,4}$ 9.1 Hz, and $J_{4,5}$ 1.0 Hz). The assignments were corroborated by selective homonuclear decouplings; $\delta(^{13}C)$ (25 MHz, $CDCl_3$) 8.2 (C-6), 20.7 and 20.9 (2 $COCH_3$), 39.2 (C-4), 55.8 (OCH_3), 68.0, 68.6, and 70.1 (C-2, C-3, C-5), 97.1 (C-1), and 169.5 and 169.8 (2 $COCH_3$). Hydrogenation of the diacetate of compound (5) with 10% palladium on carbon in ethanol containing an excess of triethylamine afforded *methyl 2,3-di-O-acetyl 4,6-dideoxy-α-D-*xylo*-hexopyranoside*, $\delta(^1H)$ (100 MHz, $CDCl_3$) 1.21 (d, 3 H, 6-H), 1.56 (m, 1 H, 4-H_{ax}), 2.02 and 2.10 (2 s, each 3 H, 2 $COCH_3$), 2.20 (m, 1 H, 4-H_{eq}), 3.38 (s, 3 H, OCH_3), 3.95 (m, 1 H, 5-H), 4.72—4.90 (d, dd, 2 H, 1-H, 2-H), and 5.20 (m, 1 H, 3-H). The assignments were corroborated by selective homonuclear decouplings.

Methyl 3,6-Dibromo-3,6-dideoxy-α-D-allopyranoside.—A mixture of methyl α-D-glucopyranoside (0.50 g, 2.57 mmol), triphenylphosphine (2.70 g, 10.3 mmol), and tribromoimidazole [6,15] (1.57 g, 5.15 mmol) in toluene–acetonitrile (2 : 1; 55 ml) was stirred at 75 °C for 1 h and then at 110 °C for 4 h, cooled, and concentrated. The product was purified by chromatography on a silica-gel column [toluene–ethyl acetate (3 : 1)] to yield the chromatographically pure title compound (620 mg, 75%) with a ^{13}C n.m.r. spectrum identical with that of a reference sample.[6]

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