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Note

Dimeric 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl

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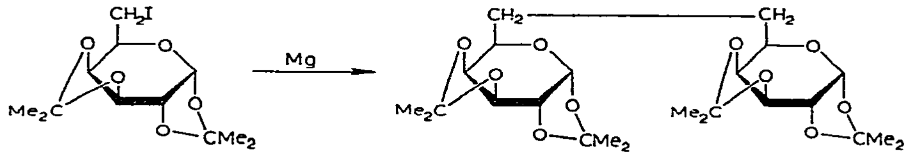
Although reactions of carbohydrates with Grignard reagents have been reviewed[1], the preparation of Grignard reagents from halo sugars has not been reported. This paper describes the reaction of magnesium with 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**1**), 6-deoxy-6-iodo-1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose (**2**), and methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-methyl-α-D-glucopyranoside (**3**) in attempts to prepare the corresponding Grignard reagents.

A mixture of compound **1** and magnesium in tetrahydrofuran was refluxed for 18 h. Analysis of the mixture by t.l.c. showed three major components: unreacted **1**, 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, (**4**), and a component of lower R_F value (**5**). Separation by chromatography yielded pure **5** as a colorless syrup, which crystallized on storage. N.m.r., i.r., and m.s. data indicated that **5** was the 12-carbon sugar, 6,7-dideoxy-1,2:3,4:9,10:11,12-tetra-*O*-isopropylidene-α-L-*galacto*-α-D-*galacto*-dodeca-1,12-dialdo-1,5:8,12-dipyranose. Binkley and Binkley[2] proposed this structure for one of the minor components isolated from the photolysis of **1**. The mass spectrum of **5** showed a high-mass peak at *m/e* 486, that corresponds to the molecular weight of the proposed structure. The remainder of the major peaks are those expected for this structure by comparison with the mass spectrum of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[3]. The n.m.r. spectrum of **5** gave a sharp doublet at τ 4.51 assigned to H-1; three doublets of doublets at τ 5.44, 5.75, 5.87; multiplets at τ 6.26 and 8.30; and peaks at 8.52, 8.58, 8.69, 8.71. Decoupling at H-1 collapsed the doublet of doublets at 5.75 to a doublet, and this absorption was assigned to H-2. From consideration of the coupling constants, the absorption at τ 5.44 was assigned to H-3 and that at 5.87 to H-4. Decoupling at τ 6.26 reduced the multiplicity at 8.30, and decoupling at τ 8.30 gave a broad singlet at 6.26. From the peak areas and the coupling constants, the absorption at τ 6.26 was assigned to H-5 and that at 8.30 to H-6. Compound **5** was recovered in 46% yield by chromatographically separating and recycling unreacted **1** four times. The reaction of **1** with Mg in the absence of molecular sieves gave **5** in lower yield.



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Treatment of **3** with magnesium gave a complex mixture. After several chromatographic separations, a chromatographically pure, colorless syrup was obtained that crystallized on being kept, but the low yield prevented complete characterization. The complexity of the n.m.r. spectrum gave inconclusive information as to the exact structure of the product. However, g.l.c.–m.s. analysis showed the compound to behave as a single component that gave the fragmentation pattern expected for the 6-deoxy dimer by comparison with the mass spectra of other *O*-methylated sugars[4].

Similar treatment of **2** with magnesium again gave a complex mixture, and attempts to isolate the expected dimer were unsuccessful.

Although the formation of dimeric products may have proceded via a Grignard reagent, addition of carbon dioxide to the mixture of **1** and magnesium gave none of the expected acid. Therefore, reaction with the second mole of **1** must be rapid or simultaneous. Separation of the reaction products from **2** and **3** by chromatography gave mixtures having R_F values expected for dimers and trimers. I.r. analysis of the mixtures showed no hydroxyl-group and only weak carbonyl absorption. Therefore, these products are considered to be dimers and trimers of intermediates formed by rearrangement of the protecting groups, probably by free-radical mechanisms.

Methods for preparation of several precursors of **1**, **2**, and **3** were improved. For example, methyl 6-*O*-tosyl-α-D-glucopyranoside was converted into methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-methyl-α-D-glucopyranoside in a one-step reaction.

EXPERIMENTAL

General. — I.r. spectra were recorded as films with a Beckman IR-33 spectrophotometer*. N.m.r. spectra were recorded with a Varian HA-100 n.m.r. spectrophotometer, with chloroform-*d* as the solvent and tetramethylsilane as the internal reference-standard. Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Rudolph polarimeter.

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

Silica Gel G was the adsorbent for t.l.c. and sulfuric acid (5%) in methanol, the visualizing agent. Desorption chromatography was conducted with silicic acid (Mallinckrodt, 100 mesh) as the stationary phase and hexane–ethyl acetate as eluant.

*6-Deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**1**). — To a mixture of sodium iodide (50 g) in *N,N*-dimethylformamide (50 ml) at 135° was added 6-deoxy-1,2:3,4-di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose[5] (10.0 g). The solution was kept for 30 min at 130–140°, and then cooled to 90° and diluted with water (200 ml). An almost colorless syrup precipitated. The supernatant liquid was decanted, and the syrup washed with water (25–30 ml). On being kept, a light-yellow crystalline precipitate separated from the solution, and it gave identical i.r. and t.l.c. behavior as an authentic sample[5] of **1**. The product was recrystallized from methanol (6.3 g, 70% yield).

Reaction of **1** *with magnesium.* — A flask (200 ml) containing magnesium (8.1 g) and molecular sieves (4.0 g) was flame-dried. After cooling, **1** (8.0 g) and tetrahydrofuran (30 ml) were added. The mixture was warmed, and a mixture of magnesium (0.5 g), ether (~4 ml), and 1,2-dichloroethane (0.5 g) that was reacting vigorously, was added. The mixture was refluxed for 24 h, and then diluted with ether (100 ml), and transferred to a separatory funnel. After the ether solution had been washed successively with aqueous sodium hydrogencarbonate, sodium thiosulfate, and water, it was dried with (sodium sulfate). The ether was evaporated off, and the resulting colorless syrup was chromatographed on silicic acid with hexane–ethyl acetate eluant to give compound **1** (4.3 g, R_F 0.8), 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.1 g, R_F 0.7) and compound **5** (0.5 g, R_F 0.3). The t.l.c. eluant was 4:1:3 carbon disulfide–ethyl acetate–hexane. Syrupy **5** crystallized on storage and was recrystallized from methanol; m.p. 107–109°, $[\alpha]_D^{25}$ $-77°$ (*c* 1, chloroform); *m/e* 486 (M), 471 (M−15), 370, 355, 295, 267, 227, 171, 163, 155, 153, 141, 113, 100 (base peak), 81, 71, 59, 43, 28; n.m.r.: τ 4.51 (d, H-1, H-1′), 5.44 (dd, H-3, H-3′), 5.75 (dd, H-2, H-2′), 5.87 (dd, H-4, H-4′), 6.26 (m, H-5, H-5′), 8.30 (m, H-6, H-6′), 8.52, 8.58, 8.69, and 8.71 (CMe_2).

Anal. Calc. for $C_{24}H_{38}O_{10}$: C, 59.28; H, 7.82. Found: C, 59.4; H, 8.1.

Another preparation in which recovered **1** was recycled four times gave **5** in 46% yield.

*1,2:3,5-Di-*O*-isopropylidene-6-*O*-tosyl-α-*D*-glucofuranose.* — To an aqueous solution of acetic acid (80 ml, 30%) was added 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and the solution was kept for 20 min at 55°. The solvent was evaporated during ~15 min at 62° under diminished pressure. The resulting white, crystalline solid was recrystallized from ethyl acetate (15.8 g) and was identical to an authentic sample of 1,2-di-*O*-isopropylidene-α-D-glucofuranose[6] by comparison of i.r., t.l.c., m.p., and mixed m.p. (93% yield).

This product was then converted into 1,2:3,5-di-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranoside by the method described by Coxon[7].

*6-Deoxy-6-iodo-1,2:3,5-di-*O*-isopropylidene-α-*D*-glucofuranose* (**2**). — To a solution of 1,2:3,5-di-*O*-isopropylidene-6-tosyl-α-D-glucofuranose (4.8 g) in *N,N*-

dimethylformamide (150 ml) was added sodium iodide (15 g). The resulting mixture was kept for 3 h on a steam bath and then cooled to 40°, whereupon water (250 ml) was added. The mixture was extracted three times with ether and the ether washed with water. The ether solution was dried with (sodium sulfate) and the solvent evaporated under diminished pressure to give a light-yellow syrup. The syrup was chromatographed on silicic acid with hexane–ethyl acetate as eluant. The major product (4.3 g) was isolated as a syrup, which crystallized on storage. Recrystallization from methanol–water gave compound **2** as a white, crystalline solid (3.88 g, 91%) m.p. 61–63°, $[\alpha]_D^{25}$ +32.8° (*c* 0.4, ethanol); lit.[7] $[\alpha]_D^{32}$ +34.4°, +30.9° (in ethanol).

Reaction of **2** *with magnesium.* — A flask containing magnesium (2.0 g) was flame-dried, and molecular sieves (2.0 g, type 4A) and tetrahydrofuran (10.0 ml) were then added. After the introduction of **2** (1.5 g), a mixture of 1,2-dichloroethane (0.5 g), magnesium (0.5 g), and ether (~4 ml) that was vigorously reacting, was added. The mixture was refluxed for 3 h under nitrogen. T.l.c. of the mixture (4:1:3 carbon disulfide–ethyl acetate–hexane) showed seven components. The R_F values of the products were all much lower than that of compound **2**. I.r. analysis indicated only weak OH and C=O absorption, indicating no loss of protecting groups. Chromatographic separation of the mixture into the individual components was unsucessful.

*Methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-methyl-α-*D*-glucopyranoside* (**3**). — A mixture of methyl 6-tosyl-α-D-glucopyranoside (10 g), methyl iodide (40 ml), barium oxide (50 g), barium hydroxide octahydrate (4.0 g), and *N,N*-dimethylformamide (100 ml) was kept for 2 h on a steam bath after which it was cooled and diluted with chloroform (1,000 ml). The insoluble solids were removed by centrifugation and washed twice with chloroform (400-ml portions). The supernatant liquids were combined and extracted with dilute hydrochloric acid (100 ml), 5% sodium hydrogencarbonate (100 ml), and twice with 1% sodium thiosulfate (100 ml). The yellow chloroform solution was concentrated to 200 ml and then extracted twice with 200-ml portions of water. The organic solution was evaporated to a yellow syrup that was dissolved in methanol and decolorized with activated charcoal. The resultant. colorless solution was concentrated and cooled; it gave crystalline **3** (6.0 g) after nucleation with **3**.

Reaction of **3** *with magnesium.* — A flask containing magnesium (2.0 g) was flame-dried and then cooled. Molecular sieves (2.0 g, type 4A), tetrahydrofuran (20 ml), and **3** (1.2 g) were added, and the mixture was refluxed for 24 h. The solution was decanted into a separatory funnel and the unreacted magnesium washed with ether (100 ml), and the washings were combined with the tetrahydrofuran solution. The ether solution was washed with M hydrochloric acid (50 ml), and then with 5% sodium hydrogencarbonate and 1% sodium thiosulfate (100 ml), and finally with water (50 ml). The ether solution was then dried (sodium sulfate) and the solvent evaporated to give a yellow syrup. The syrup was chromatographed on silicic acid with chloroform as eluent to give several fractions. The fraction having R_F ~0.35 (4:1:3 carbon disulfide–ethyl acetate–hexane) crystallized on storage (yield 0.05 g), m.p. 73–75; *m/e* 373, 343, 337, 319, 231, 189, 167, 157, 145, 141, 131, 129, 128, 127, 115, 101, 97, 88 (base peak), 75, 71, 55, 45, and 41.

Anal. Calc. for $C_{20}H_{38}O_{10}$: C, 54.8; H, 8.67. Found: C, 55.4; H, 8.63.

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