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Unusual Behaviour of Aryl 2-Deoxy-D-galactosides Under Lewis Acid Catalysis: A Facile Entry to C-Aryl 2-Deoxy-D-glycosides and Bridged Chiral Benzopyran Derivatives#.

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Abstract: The unusual behaviour of aryl 2-deoxy-D-galactopyranosides yielding two different products with $BF_3.Et_2O$ under different concentrations is reported.

2-Deoxy sugars are present in numerous biologically active natural products[1] such as compactin, olivomycin, mithramycin, daunomycin, calicheamycin etc. Normally, preparation of 2-deoxy glycosides from protected glycals under acid conditions results in the formation of rearranged products[2]. However, the reported synthesis of 2-deoxy galactosides using the anhydrous H^+ resin does not deal with phenyl galactosides. The application of triphenylphophonium hydrobromide mediated synthesis of aryl 2-deoxy-D-glycosides has not been applied to galactals[4] and the direct preparation of phenyl galactosides using *p*-toluenesulphonic acid[5] did not work out in our hands. During the course of our continued efforts towards the synthesis of C-aryl glycosides[6], we stumbled upon a convenient method for the formation of phenyl 2-deoxy-D-galactosides, which we report herein.

With the expectation of obtaining the 2,3-unsaturated phenyl galactopyranosides (i.e., the Ferrier products)[7], which are potential substrates for C-arylglycoside *via* 'O' to 'C' migration, we carried out the reaction of tri-O-acetyl-D-galactal with *p*-cresol in refluxing chlorobenzene. In the event, we isolated a viscous liquid product in 77% yield which upon column chromatography afforded a gummy solid. This product was analysed by spectral and elemental analysis to be *p*-cresyl 2-deoxy-*α*-D-galactopyranoside[5,8] **2a** which was quite unexpected in the absence of an

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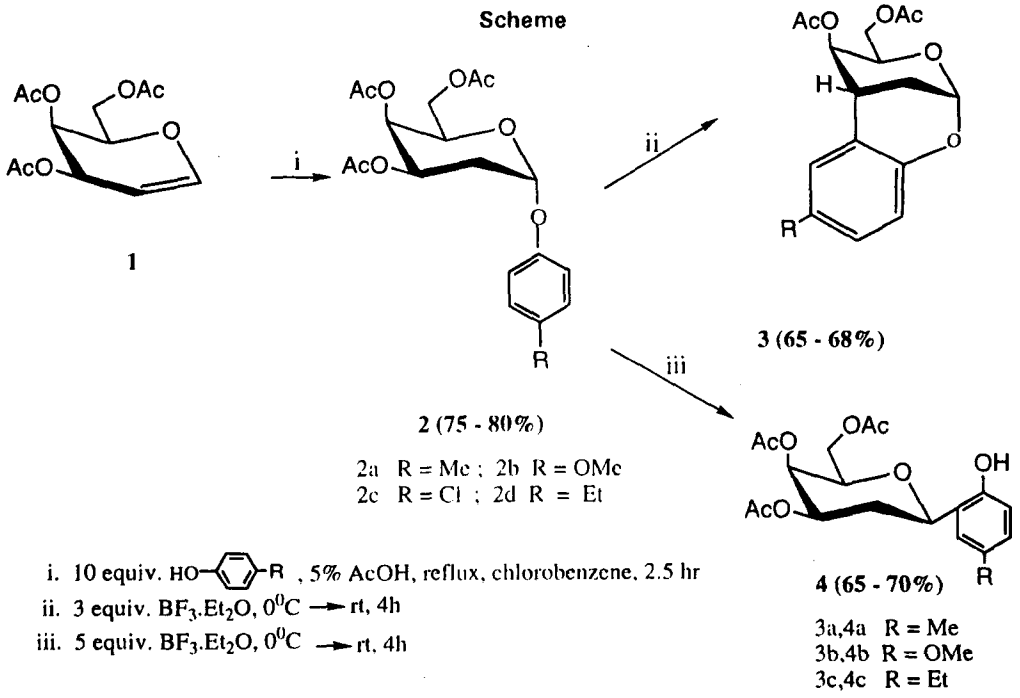
added acid catalyst. On closer scrutiny, we found that the chlorobenzene used was contaminated with acetic acid, which might have been responsible for the formation of the 2-deoxy glycoside **2a**. After several trials, we arrived at conditions by which we could obtain a maximum yield of 75-80% of aryl 2-deoxy-D-galactopyranoside **2** simply by employing 5% glacial acetic acid (v/v) in refluxing chlorobenzene (Scheme).

Scheme



The generality of this reaction was successfully tested with a few other para- substituted phenols[8]. The elemental analysis and spectral data of the products **2a-d** were in accordance with the assigned structure (in all the cases the formation of β-glycoside was not detected by tlc or nmr (400 MHz) of the crude reaction product). Surprisingly, under these conditions, tri-O-acetyl-D-glucal was found to provide exclusively the "normal" Ferrier product, viz., the 2,3-unsaturated glycoside.

Having prepared a series of aryl 2-deoxy-D-galactosides, we then attempted to bring about 'O' to 'C' migration[9,10a-e] of the aryl group using $BF_3.Et_2O$ with a view to synthesise C-aryl 2-deoxy-D-glycosides. The facile 'O' to 'C' rearrangement of aryl 2,3-dideoxy-hex-2-enopyranosides[6] brought about by Lewis acid catalysis prompted us to study the behaviour of the aryl 2-deoxy-D-glycosides **2a-d** under these conditions.

Exposure of *p*-cresyl 2-deoxy-D-galactopyranoside **2a** to three equivalents of $BF_3.Et_2O$ in dichloromethane at 0°C and then at room temperature for 4 h furnished a viscous liquid in 65% yield whose structure has been established by elemental analysis and spectral data[11] to be the bridged glycosyl benzopyran **3a** (scheme).

The generality of this transformation was tested with some phenyl 2-deoxy-D-galactopyranosides[8]. No precedence could be found in the literature for this kind of cyclisation involving aryl glycosides. Lewis acid catalysed reaction of aryl 2-deoxy-D-glycosides has been reported to give mainly[10d,e,12] the C-aryl glycosides without any particular application to galactose derivatives.

We tried various conditions in order to obtain C-aryl glycoside from **2a**. Finally, with five equivalents of the lewis acid, the reaction could be diverted to C-aryl galactopyranoside **4a** in 65% yield and stopped at that stage [13] (scheme).

The assignment of β-configuration for **4a** is based on ^1H nmr (400 MHz) data in accordance with literature reports on similar compounds[10a-e,11,14]. Thus, the anomeric proton in **4a** resonated at δ4.7, as doublets of a doublet with $J_{1,2a}$ = 12.5 Hz and $J_{1,2e}$ = 2.5Hz.

In the case of *p*-chlorophenyl 2-deoxy-α-D-galactoside **2c** neither cyclisation nor any rearrangement was found to occur even after six hours. The 'O' to 'C' migration process was found to occur also with **2b** (*p*-OMe) and **2d** (*p*-Et)[8]. The products were thoroughly characterised by spectral and elemental analysis. While the reasons behind the marked influence of Lewis acid concentration in determining the outcome of the reaction are unclear at present, our study, besides bringing out a useful procedure for the preparation of aryl-2-deoxy-D-galactosides, also demostrates an unusual dual behaviour of these compounds with respect to $BF_3.Et_2O$. By changing the catalyst concentration, we are able to obtain directly either the C-aryl glycoside or the bridged glycosyl benzopyran dereivatives[15]. A detailed study on the effect of varying the mole proportion of the lewis acid on the course of the this reaction is underway.

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8. All compounds gave satisfactory spectral and elemental analysis.The yields and $[\alpha]_D$ of all the compounds are given here.
   2a: 77%, 138.6° (*c*, 0.9); **2b**: 80%, 144.3° (*c*, 1.5); **2c**: 75%, 125.2° (*c*, 1.5), **2d**: 78%, 130.5° (*c*, 1.3); **3a**: 65%, 31.2° (*c*, 0.3); **3b**: 68%, 54.7° (*c*, 0.3), **3d**: 67%, 45.9° (*c*, 0.3), **4a**: 70%, 20.5° (*c*, 0.3), **4b**: 65%, 24° (*c*, 0.3); **4d**: 68%, 22.2° (*c*, 0.4). All rotations were measured at the optimum temperature of 25 - 28° C and the solvent used was chloroform.
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11. Elemental analysis for **3a**: Observed C 63.63, H 6.12; Calculated for $C_{17}H_{20}O_8$ C 63.75, H 6.25. ^{1}H nmr (400 MHz) for **3a**: δ 1.65-1.75 (m, 1H, H_{2e}), 2.00 (s, 3H, -OAc), 2.2 (s, 3H, -OAc), 2.3 (s, 3H, Ar-CH_3), 2.45 (td, 1H, $J_{1,2e} = J_{2e,3} = 2.7$ Hz, $J_{2e,2e} = 13.3$ Hz, H_{2e}), 3.25 (bs, 1H, H_3), 3.95-4.15 (m, 3H, H_5, H_{6a} and H_{6b}), 4.85 (bs, 1H, H_4), 5.65 (bs, 1H, H_1), 6.85 (d, 1H, J = 8 Hz, $H_{6'}$), 7.00 (s, 1H, $H_{3'}$), 7.05 (d, 1H, J = 8 Hz, $H_{5'}$). The ^{13}C nmr for **3a**: δ 20.42 (q), 20.81 (q), 21.08 (q), 23.53 (t), 32.48 (d), 63.22 (t), 67.12 (d), 70.73 (d), 92.96 (d), 115.54 (d), 121.87 (d), 129.55 (d), 129.72 (s), 130.49 (s), 152.70 (s), 170.26 (s), 170.66 (s).
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13. Elemental analysis for **4a**: Observed C 59.75, H 6.20, Calcuated for $C_{19}H_{24}O_8$ C 60.0, H 6.31. The Ir (cm^{-1}): 3440, 3040, 1730, 1510, 1380, 1200, 1110, 1040, 1000, 980, 910, 840, 810. ^{1}H nmr (400 MHz) for **4a**: δ 2.00 (s, 3H, -OAc), 2.05-2.07 (m, 1H, $H_{2'e}$), 2.08 (s, 3H, -OAc), 2.18 (s, 3H, -OAc), 2.3 (s, 3H, Ar-CH_3), 2.35 (q, 1H, $J_{1',2'e} = J_{2'e,2'e} = J_{2'e,3'} = 12.5$ Hz, $H_{2'e}$), 4.00 (t, 1H, $J_{5',6'a} = J_{5',6'b} = 6.3$ Hz, $H_{5'}$), 4.15-4.2 (m, 2H, $H_{6'a}$ and $H_{6'b}$), 4.7 (dd, 1H, $J_{1',2'e} = 12.5$ Hz, $J_{1',2'e} = 2.5$ Hz, $H_{1'}$), 5.15 (ddd, 1H, $J_{2'e,3'} = 12.5$ Hz, $J_{2'e,3'} = 5$ Hz, $J_{3',4'} = 2.5$ Hz, $H_{3'}$), 5.4 (d, 1H, $J_{3',4'} = 2.5$ Hz, $H_{4'}$), 6.82 (d, 1H, $J_{5,6} = 8$ Hz, H_6), 6.84 (s, 1H, H_3), 7.02 (d, 1H, J = 8 Hz, H_5), 7.24 (s, 1H, Ar-OH, exchangeable with D_2O). ^{13}C nmr for **4a**: (ppm) 20.46 (q), 20.70 (q), 20.84 (q), 31.21 (t), 62.48 (t), 66.09 (d), 69.31 (d), 75.05 (d), 78.54 (d), 117.24 (d), 124.09 (s), 127.16 (d), 129.28 (s), 130.19 (d), 152.90 (s), 170.11 (s), 170.19 (s), 170.55 (s).
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