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Unexpected C_3 Arylation Of 3,4,6-tri-O-methyl-2-C-formylglycals : A Simple Route To 3-C-arylhexoses

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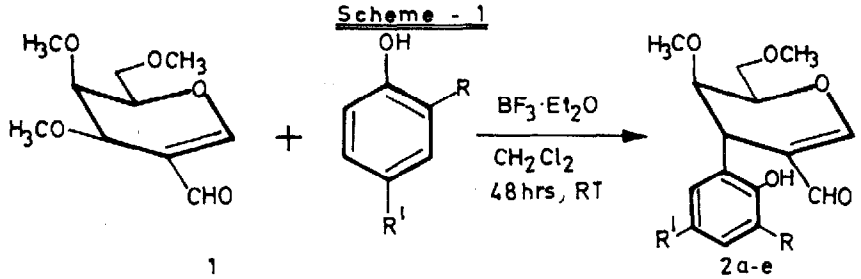
ABSTRACT : Unusual regiochemistry in the nucleophilic reaction of substituted 2-C-formylglycals with phenols under Lewis acid catalysis leading to 3-C-arylhexoses is reported.

C-Arylglycosyl compounds have received wide attention in recent years particularly since the isolation of new classes of antitumor compounds such as ravidomycin, vineomycin etc.,[1]. A simple route for C-arylglycosides is the direct C-alkylation of phenols at the anomeric carbon of carbohydrates bearing a good leaving group[2] or Lewis acid catalysed[3] or transition metal complex promoted[4] 'O' to 'C' rearrangement of O-arylglycosides. Prompted by these reports, we explored the possibility of a concise synthesis of C-arylglycosides by Michael addition of phenols to the readily available 2-C-formylglycals[5].

Our initial attempts to effect a Michael reaction between tri-O-methyl-2-C-formylglycal 1 and phenols under standard conditions[6,7] were unsuccessful. Even after refluxing in chlorobenzene as such or in the presence of triethylamine, no reaction was observed. Hence, we investigated the acid-catalysed[8] Michael addition of phenols to 1 expecting the formation of a C-glycoside by C-arylation at the anomeric carbon. In the event, we encountered an unexpected reversal of reactivity at the C_3 and C_1 centres in 2-C-formylglycal 1, leading to a stereoselective route for the synthesis of hitherto unknown 3-C-arylglycals which we report in this communication. Thus, treatment of a mixture of 1 and p-cresol in dichloromethane with $BF_3.Et_2O$ for 48 hours at room temperature, gave a viscous liquid which was purified by column chromatography (Scheme 1).

Scheme - 1



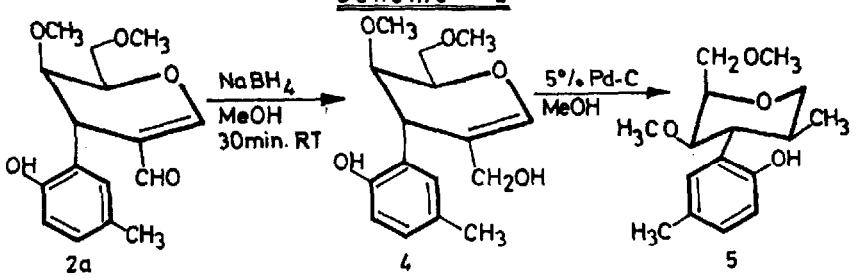
1 2a-e

The product 2a analysed for $C_{16}H_{20}O_5$ and its IR spectrum showed bands at 3310 cm^{-1} (OH), 1620 cm^{-1} and 1660 cm^{-1} (-C=C-CHO) indicating the presence of phenolic and α,β-unsaturated aldehyde units. Upon acetylation, 2a afforded a solid monoacetate (m.p. 80°C). An examination of the ^1H nmr and ^{13}C nmr spectra of the product revealed the incorporation of p-cresol moiety in addition to the intact formylglycal unit. The ^1H nmr spectrum displayed signals at δ9.4(1H, s, CHO), 8.1(1H, bs, OH), 7.7(1H, s, H_1), 6.5(2H, m, H_4' and H_6'), 6.0(1H, d, J=7.3Hz, H_3'), 4.6(1H, s, H_4), 4.2(1H, dd, $J_{5,6a}$=5.9Hz, $J_{5,6b}$=8.8Hz, H_5), 3.8(1H, dd, $J_{5,6b}$=8.8Hz, $J_{6a,6b}$=11.8Hz, H_{6b}), 3.65(1H, s, H_3), 3.5(1H, dd, $J_{5,6a}$=5.9Hz, $J_{6a,6b}$=11.8Hz, H_{6a}), 3.35 & 3.55(6H, 2s, OMe) and 2.1(3H, s, Me). It is evident that this product was neither the expected 'C' nor the 'O' Michael adduct or any of the allylic rearrangement products[2]. The loss of one of the $-OCH_3$ groups, the persistant formylglycal unit and the spectral data suggested its structure to be 4,6-di-O-methyl-1,5-anhydro-3-C-(2'-hydroxy-5'-methylphenyl)-2-C-formyl-2,3-dideoxy-D-xylo-hex-1-enitol 2a.

The assigned structure was also in accordance with the ^{13}C nmr spectrum which showed signals at δ192.13(d), 167.66(d), 152.07(s), 128.30(d), 128.26(d), 127.97(s), 124.33(s), 118.12(s), 114.66(d), 76.01(d), 74.89(d), 72.26(t), 59.30(q), 57.28(q), 31.61(d), 20.56(q). Particularly significant was the signal at δ31 in the ^{13}C nmr spectrum of 2a, not observed in 1, which could be unequivocally assigned to C_3 (Ar-C) while the signals at δ190, 167 and 118 correspond to the formylglycal moiety. The pseudo-axial orientation of the aryl group at C_3 in 2a was established by ^1H nmr coupling constants : $J_{(3e,4e)} \simeq 0$; for comparison, in 1 $J_{(3a,4e)}$ = 3.7 Hz.

The structure of 2a was further confirmed by the following transformations: selective reduction of 2a with $NaBH_4$ gave 4 whose ^1H nmr spectrum showed the olefinic proton at δ6.8, typical of a glycal anomeric proton whereas it is normally observed around δ5.5-6.0 for a 'Ferrier' product[2]. Subsequent reduction of 4 with 5% Pd-C/H_2 furnished 5, a product of both hydrogenation and hydrogenolysis, as a liquid whose spectral data were in accordance with the assigned structure. From the ^1H nmr spectral data given below, it is evident that 5 exists in the alternate chair ($^1C_4$) conformation[6] (Scheme 2).

Scheme - 2



For 5, relevant ^{1}H nmr spectral data are δ0.7(3H, d, J=6.35Hz, Me), 2.29(4H, m, H_2 and aromatic Me), 2.81(1H, t, J=11.2Hz, H_3), 3.22(3H, s, OMe), 3.5(5H, m, H_4, H_{1a} and OMe), 3.6(1H, dd, $J_{5,6a}$=2.9Hz, $J_{6a,6b}$=10.7Hz, H_{6a}), 3.7(1H, dd, $J_{1e,2}$=4.9Hz, $J_{1e,1a}$=11.7Hz, H_{1e}). Partially decoupled ^{13}C nmr spectrum of 5 showed two triplets at δ66.2 and 67.12 which confirmed that the double bond is located only between C_1 and C_2 in the unreduced compound **4**.

Extension of this reaction to various phenols yielded the corresponding 3-C-aryl derivatives **2b-d** (Table 1). Monitoring the reaction in the case of p-cresol and **1** by tlc and nmr did not show any evidence for the intermediacy of 'O' Michael adduct or 'O' Ferrier product. In the case of the reaction of p-chlorophenol with **1**, it was possible to isolate another product by column chromatography **3**, albeit in minor amount, in addition to the 3-C-chlorophenyl product **2d**. The spectral data of **3** indicated it to be 4,6-di-O-methyl-1,5-anhydro-3-O-(4'-chlorophenyl)-2-C-formyl-2-deoxy-D-xylo-hex-1-enitol. Exposure of **3** to $BF_3.Et_2O$ in CH_2Cl_2 converted it to **2d**. Treatment of the C_3 epimer of **1**, viz., **6** with $BF_3.Et_2O$ also afforded only **2a** and not the product of S_N2 substitution (Scheme 3).

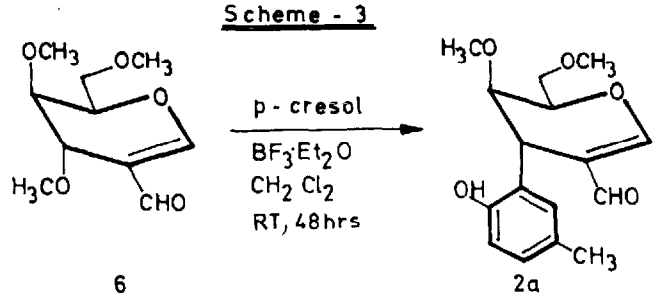
In the light of these findings, it can be suggested that the reaction probably goes through the Lewis acid catalysed formation of allylic cation, followed by preferential attack of phenol from the axial side at C_3 through oxygen and a subsequent 'O' to 'C' migration assisted by $BF_3.Et_2O$. A competitive direct C-arylation at C_3 of the allyl cation by the phenol cannot be excluded with the data on hand.

Table 1

Entry	Compound No.	R	R'	Yield* (%)	$[\alpha]_D$, $CHCl_3$
1	2a	H	Me	50	+197.98(c,1.02)
2	2b	H	OMe	55	+162.68(c,1.05)
3	2c	H	Et	50	+146.86(c,0.65)
4	2d	H	Cl	40	+142.72(c,1.35)
5	2e	OMe	Me	55	+161.55(c,1.62)

* Represents isolated yield. All compounds gave satisfactory spectral and analytical data

Scheme - 3



6 2a

It may be noted here that related glycals such as 2-C-cyanoglycals[6] and 2-C-arylsulfonylglycals[7] have not been studied under Lewis acid catalyzed Michael conditions. The unusual reactivity at C_3 in 2-C-formylglycals is in remarkable contrast to the known reactivity pattern of glycals[2] which show pronounced tendency to undergo nucleophilic attack at the anomeric carbon in preference to C_3, under Lewis acid catalysis. Also, seldom $-OCH_3$ has been reported to be a leaving group[9] in such reactions, most of the reactions having been carried out only on the corresponding O-acetyl derivatives[2]. Infact, tri-O-methylgalactal itself was found to be quite unreactive when treated with p-cresol under the above reaction conditions, in the present study. There are hardly any reports on 3-C-arylcarbohydrates[10]. In view of the growing interests on C-arylglycosides, and of the paucity of reports on the isomeric 3-C-arylhexoses[11], our present observations provide a stimulus to explore the chemistry of the 3-C-arylhexopyranoses.

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