Electrophilic Substitution of Aromatic Compounds by Unsaturated Sugar Derivatives

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Hexenopyranosyl Carbocations, Pent-2-enopyranosyl-4-ulosyl Carbocations

Glycosylic carbocations. A hard base. As the next carbocation-forming unsaturated sugar derivative 1-0-benzoyl-2,3-dideoxy-DL-pent-

Glycosyl halides or esters are capable to alkylate aromatic substrates in the presence of Lewis acids [1]. This reaction gives a simple synthetic access to C-glycosylic compounds, including biologically important C-nucleosides [2]. It is assumed that glycosyl carbocation intermediates in these alkylations.

It has been noticed that double bond in position 2,3- of the pyranoside ring facilitates the formation of the corresponding glycosyl carbocation [3], and in consequence 1,2- or 2,3-unsaturated monosaccharide derivatives should be particularly active as alkylation species. However no reaction of such sugar substrates with aromatic compounds have been reported so far. Therefore, we decided to examine the reactivity of unsaturated monosaccharides toward aromatic substrates susceptible to electrophilic alkylation under Friedel-Crafts reaction conditions.

In our experiments easily available 3,4,6-tri-0-acetyl-2,3-dideoxy-D-hex-1-enitols (1) and (2) were taken as a source of glycosil carbocations. A considerable number of nuclophile allylic displacement reactions of 1 and 2 have been examined and there is a general agreement that bidentate carbocation 3 intermediates in these reactions. It seems, that regio- and stereoselectivity of such reactions depends rather strongly on the kind of nucleophile used.

For example, reaction of 1 with aliphatic alcohols is remarkably selective, leading exclusively to alkyl a-hex-2-enopyranosides [4] while all four possible products, resulting from nonsterespecific substitution in positions C-1 and C-3, are formed in the reaction with azide anion [5].

The reaction of 1 with an excess of methoxybenzene in the presence of stannic chloride afforded a crystalline product, which on the basis of the spectral and analytical evidence was assigned 1'-[4,6-di-0-acetyl-2,3-dideoxy-a-D-erythro-hex-2-enopyranosyl]-4'-methoxybenzene [4] structure. The configuration at C-1 was deduced from the 1H NMR spectrum. The signal corresponding to H-1 displayed a broad singlet at δ 5.19, H-2 and H-3 formed a multiplet centered at δ 5.88 and H-4 was recorded as a characteristic pair of doublets with spacings J12 = 9.0 Hz and J34 = 2.7 Hz. These spectral features and also specific rotation value strongly resemble the data for alkyl 2,3-dideoxy-a-D-erythro-hex-2-enopyranosides [4]. Under the same reaction conditions 2 afforded chromatographically homogeneous oily mixture of products, identified on examination of its 1H NMR spectrum as 1'-[4,6-di-0-acetyl-2,3-dideoxy-a,β-D-threo-hex-2-enopyranosyl]-4'-methoxybenzene (5) and (6). From the signals of olefinic protons with the following coupling constants: J12 = 3.2, J13 = 1.8, J23 = 10.0 and J34 = 5.0 Hz, configuration α was assigned to the component comprising about 35% of the mixture. We feel that lack of 3-substituted pyranosides among the reaction products obtained from 1 and 2 reflects kinetic control of the alkylation process. Alternative explanation of the observed selectivity, based on HSAB principle [6], indicates that p-anisyl anion should be regarded as a relatively hard base.

As the next carbocation-forming unsaturated sugar derivative 1-0-benzoyl-2,3-dideoxy-DL-pent-
2-enopyranos-4-ulate (7), a substrate in synthesis of racemic ribose [7] and some disaccharides [8], was taken. Its alkylating properties were earlier observed in Lewis acid catalyzed reaction with phenols [9]. Compound 7 reacted smoothly with methoxybenzene in the presence of stannic chloride yielding the expected C-glycosyl derivative 9 in good yield. Analogously, the reaction of 7 with 1,4-dimethoxybenzene led to compound 10. However, when 2-methyl-furan was employed as the aromatic substrate in the reaction with 7, instead of the benzoate group displacement formation of an adduct was observed, although in low yield. The use of milder acidic catalyst, namely zinc chloride, allowed to obtain the adduct identified as 1-O-benzoyl-2-[2'-5' methylfuryl]-2,3-dideoxy-a-DL-glycero-pent-4-ulate (11) in reasonable quantity. The structure unequivocally followed from analytical and spectral data. Well resolved 100 MHz 1H NMR spectrum of 11 displayed signals corresponding to phenyl, 2-methylfuran and pyranos-4-ulate ring protons. All signals were sharp, pointing at homogeneity of the adduct. The observed coupling constant $J_{12} = 4.5$ Hz exceeds values expected for axial-equatorial arrangement of vicinal protons thus indicating trans-disposition of the substituents at C-1 and C-2 with prepondering C4 conformation.

$$\text{11: } \text{Ar} = 2-\text{(5-methylfuran)}$$

To confirm this configurational assignment adduct 11 was reduced with sodium borohydride followed by acetylation, which afforded compound 14. 1H NMR spectrum of 14 was fully compatible with the structure and configuration indicated.

$$\text{14: } \text{Ar} = 2-\text{(5-methylfuran)}$$

In particular $J_{12} = 6.7$ Hz points clearly in the direction of trans-diaxial coupling. Similarly, the sum of the coupling constants observed for C-4 [$J = 28.3$ Hz] and values $J_{4,5a} = 7.3$ Hz and $J_{4,5a} = 4.2$ Hz indicate considerable contribution of the conformation C4 with axial protons at C-1, C-2 and C-4. The formation of adduct 11 in reaction of 7 with 2-methylfuran can be rationalized on assumption that apart from glycosyl cation 15 resulting from dissociation of C-1 substituent, another cationic species can be generated via complexation of the carbonyl group with an acidic catalyst. Apparently the carbocation 16 can not compete effectively in electrophilic substitution reaction with the glycosylic one (15), unless i. very reactive aromatic substrate is taken, or ii. another leaving group, less susceptible to dissociation as a complex with Lewis acid is placed at C-1 site.

In order to verify this assumption addition of reactive aromatic species to methyl 2,3-dideoxy-DL-pent-2-enopyranoisid-4-ulate was tried. It was found that 8 easily reacts with 2-methyl furan in the presence of zinc chloride to give chromatographically homogeneous adduct (12). However, examination of its 1H NMR spectrum revealed the presence of two isomeric adducts in comparable amounts. Apart from two signals corresponding to methoxyl group, two anomeric protons could be recognized in the spectrum. The coupling constants $J_{12} = 2.5$ and 3.7 Hz correspond to cis- and trans-arrangement of H-1 and H-2. Similarly, prolonged treatment of 8 with methoxybenzene in the presence of zinc chloride leads to formation of methyl 2,3-dideoxy-2-C-[4'-methoxybenzene]-DL-glycero-pent-4-ulate (13) in moderate yield. The presence of 1,2-cis and 1,2-trans adducts was evident from 1H NMR spectrum of 13 but the mixture could not be resolved chromatographically.

The results described here demonstrate clearly that electrophilic substitution of aromatic compounds by unsaturated sugars can be performed in good yields under relatively mild conditions, appreciably milder than those employed in the case of saturated sugars. Products obtained represent structures which can be converted into a variety of biologically interesting compounds. It seems that the potentially two-directional reactivity of 2-enopyranos-4-ulate derivatives can be controlled, by proper selection of the C-1 substituent, catalyst and the kind of aromatic compounds.

**Experimental**

3,4,6-Tri-O-acetyl-2-deoxy-D-hex-1-enitols (1, 2) [10] and pent-2-enopyranos-4-ulate derivatives (7) [7], 8 [11] were prepared as reported in the literature.
Remaining substrates were commercial grade reagents purified by distillation or crystallization before use. Melting points are not corrected, boiling points refer to air bath temperature during microscale distillations. ~H NMR spectra were recorded on JEOL-4H-100 (100 MHz) spectrometer for CDCl$_3$ solutions with TMS as internal standard. IR spectra were taken on Unicam SP-200 spectrophotometer. Optical rotations were measured with Perkin-Elmer 141 polarimeter in CH$_2$Cl$_2$ solutions [c = 1]. TC was performed on plates coated with silica gel G, Merck, and Kieselgel 230–400 mesh (Merck) was used for column chromatography.

To a solution of 1 (0.272 g, 1 mmole) in dry 1,2-dichloroethane (5 ml) anisole (0.5 ml) was added followed by two drops of stannic chloride. The reaction mixture, protected from atmospheric moisture, was kept at ambient temperature for two hours. Then methylene chloride (20 ml) was added and the mixture was washed twice with aqueous sodium carbonate and with water. After drying the solvent over MgSO$_4$ and evaporation the oily residue was applied onto silica gel column. Elution with light petroleum-ethyl acetate 9:1 afforded 4 as colorless crystals, 0.227 g, 71% yield, m.p. 101 to 102°, [α]$^D$ + 253°, ~H NMR $\delta$: 2.08, 2.12 s, 6H, 2 AcO, 3.81 s, 3H, OCH$_3$, 5.12 and 5.35 2 s, 6H, 2 3 AcO, 3.81 s, 3H, CH$_2$-OAc, 5.12 and 5.35 2 s, 6H, 2 3 AcO, 3.81 s, 3H, OCH$_3$.

1'.[4,6-di-0-acetyl-2,3-dideoxy-a-D-threohex-2-eno-pyranosyl]-4'-methoxybenzene (4)

To a solution of 1 (0.272 g, 1 mmole) in dry 1,2-dichloroethane (5 ml) anisole (0.5 ml) was added followed by two drops of stannic chloride. The reaction mixture, protected from atmospheric moisture, was kept at ambient temperature for two hours. Then methylene chloride (20 ml) was added and the mixture was washed twice with aqueous sodium carbonate and with water. After drying the solvent over MgSO$_4$ and evaporation the oily residue was applied onto silica gel column. Elution with light petroleum-ethyl acetate 9:1 afforded 4 as colorless crystals, 0.227 g, 71% yield, m.p. 101 to 102°, [α]$^D$ + 253°, ~H NMR $\delta$: 2.08, 2.12 s, 6H, 2 AcO, 3.81 s, 3H, OCH$_3$, 5.12 and 5.35 2 s, 6H, 2 3 AcO, 3.81 s, 3H, OCH$_3$, 5.12 and 5.35 2 s, 6H, 2 3 AcO, 3.81 s, 3H, OCH$_3$.

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Found C 66.51 H 6.17, 
Caled C 66.27 H 5.85.

**Methyl-2,3-dideoxy-2-C-[2'-5'-methylfuryl]-
a,ß-DL-glycero-pent-4-ulose (12)**

Obtained from 8 and 2-methylfuran in reaction catalyzed by ZnCl₂ (65%). An oil, b.p. 100°/1 torr.

IR (film): 2900, 1730, 1620, 1570, 1130, 1100, 1060, 1020, 960, 780 cm⁻¹; 1H NMR (δ): 2.30 s, 3H, CH₃, 2.70–2.91 m, 2H, H-3a, H-3e, 3.25–3.50 m, 1H, H-2, 3.47 and 3.51 s, 3H, OCH₃, 3.85–4.28 m, 2H, H-5a, H-5e, 4.92–5.00 m, 1H, H-1, J₁₂cis = 2.5 and J₁₂trans = 3.7 Hz, 5.82–6.00 m, 2H, H-3, H-4.

Found C 62.70 H 6.83, 
Caled C 62.84 H 6.71.

**Methyl-2,3-dideoxy-2-C-[4'-methoxybenzene]-
a,ß-DL-glycero-pent-4-ulose (13)**

Obtained by stirring 8 with an excess of methoxybenzene in the presence of ZnCl₂ suspended in 1,2-dichloroethane. Reaction time at room temperature: ten days. The product isolated in 47% yield as an oil b.p. 130°/1.5 torr.

IR (film): 2900, 2700, 1725, 1610, 1520, 1245, 1175, 1120, 1100, 1050, 830 cm⁻¹; 1H NMR (δ): 2.43–3.30 m, 3H, H-2, H-3e, H-3a, 3.40, 3.44, 3.79 s, 6H, 2 x OCH₃, 3.98–3.31 m, 2H, H-5e, H-5a, 4.70–4.78 m, 1H, H-1, J₂cic = 2.7 Hz, J₂trans = 4.7 Hz, 7.02 ABq, 4H, aromatic.

Found C 65.88 H 6.89, 
Caled C 66.08 H 6.83.

\[ R^1: R^1 = H, R^2 = OAc \]
\[ R^1 = OAc, R^2 = H \]
\[ R^1 = OAc, R^2 = OAc, R^3 = 4-C₆H₄OCH₃ \]
\[ R^1 = R^2 = OAc, R^3 = 4-C₆H₄OCH₃ \]
\[ R^1 = R^2 = OAc, R^3 = H, R^4 = 4-C₆H₄OCH₃ \]
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