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Note

Access to aldehydo acetals of sugars via palladium-catalyzed oxidation of α,β-unsaturated cyclic acetals

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Dedicated to Professor Dereck Horton on the occasion of his 70th birthday

Abstract

The palladium(II)-catalyzed oxidation of α,β-unsaturated cyclic acetals derived from mono- and disaccharides leads in appreciable yields to new aldehydo acetals which, overall, results in an anti-Markovnikov addition.

Keywords: Carbohydrates; Unsaturated cyclic acetals; Aldehydo cyclic acetals; Palladium-catalyzed oxidation; Wacker process

In previous papers[1–3] we reported the synthesis of various functionalized acetals of sugars, using notably a procedure described by Gelas and Horton.[4] In this framework, we took interest in the preparation of acetals bearing a carbonyl group and described in particular a synthesis of β-keto acetals.[2] Such acetals are valuable intermediates and can be used, for instance, in asymmetric synthesis. For example, a highly diastereoselective addition of organomagnesium reagents to asymmetric α-keto acetals has been recently reported in the literature.[5] However, direct synthesis of keto acetals using classical conditions of acetalation may be difficult, and the required reagents are not always easily available. As we also previously prepared[1,2] ethylenic cyclic acetals, which are interesting synthons to be used in further chemical tranformations, we thought that they could also be used for the synthesis of carbonylated cyclic acetals.

Notably, oxidation of the double bond of ethylenic acetals such as the acrylidene derivative **1** could lead to keto acetals. For this purpose, the well-known palladium-catalyzed oxidation of olefins could be used. This reaction, which is a variation of the Wacker process, is well documented in the literature.[6–8] It is generally regioselective, so terminal olefins are oxidized to methyl-substituted ketones. The reaction involves Markovnikov hydration of the complexed double bond. A few examples of the preparation of aldehydes (or their acetals) are also mentioned;[9,10] this reverse regioselection occurs in the presence of an electron withdrawing group. The nature and location of this group play an important role.

This paper describes the preliminary study of the oxidation of acrylidene cyclic acetals of mono- and oligosaccharides with palladium(II) chloride. The reaction was carried out in aqueous *N*,*N*-dimethylformamide, using benzoquinone as the palladium reoxidant. Water was added portionwise at intervals. We have observed that better yields were obtained when the reaction proceeded at room temperature during 18–24 h. The reaction was monitored by TLC and stopped by addition of water when the starting material had disappeared.

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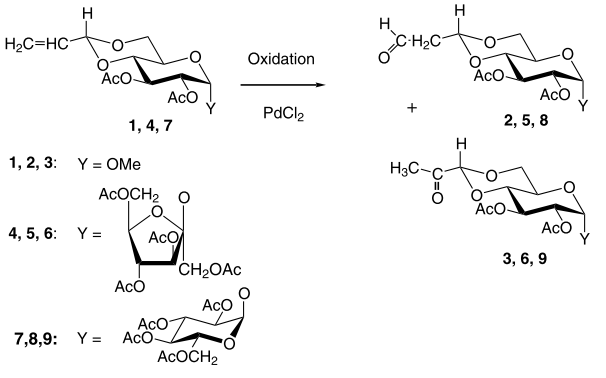
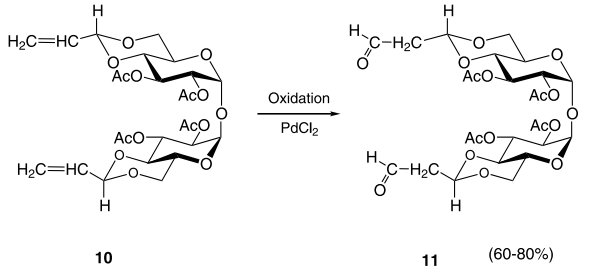
Starting from the protected methyl 4,6-*O*-acrylidene-α-D-glucopyranoside (**1**), TLC showed the formation of two compounds that could be separated by column chromatography (Scheme 1). The major product was identified as the β-aldehydo acetal **2**; the NMR spectra clearly showed characteristic signals for the acetalic carbon atom (97.5 ppm), for the aldehydic group (respectively, at 9.65 ppm [^{1}H NMR] and at 198.5 ppm [^{13}C NMR]) and for the methylene group attached to the acetalic carbon atom (respectively at 2.70 ppm [^{1}H NMR] and at 47.6 ppm [^{13}C NMR]). A minor compound that first eluted was identified by NMR spectroscopy as the α-keto acetal **3**, obtained in very low yield.

Analogous results were obtained when the reaction was performed starting from ethylenic acetals derived from sucrose **4** and trehalose **7** (Scheme 1), and finally from the trehalose diacetal **10** (Scheme 2). The corresponding aldehydes **5**, **8** and **11** were obtained in 50–80% yields and were identified by NMR spectroscopy. The keto acetals **6**, **9** and **12** were only detected in very low yields (from 2 to 5%).

Thus, starting from an α,β-ethylenic acetal of mono- or disaccharides, the oxidation reaction of the double bond at the α position of the acetal group afforded the aldehydic derivative, the nucleophilic attack of water occurring predominantly at the less-substituted position of the palladium-coordinated double bond. A similar orientation has been observed in the presence of an electron-withdrawing substituent at the α-position of the double bond.[9,10] Oxidation of the terminal olefin of



Scheme 1.



Scheme 2.

acetonides derived from allylic diols has been studied,[11] but to our knowledge, the example of a double bond attached to an acetalic carbon atom had not been previously described.

In conclusion, this work affords a synthesis of new aldehydo acetals derived from sugars and shows that α,β-ethylenic acetals are good precursors of valuable synthetic intermediates, even in the presence of a glycosidic bond. It is worthy to note that the presence of the acetal group reverses the regioselectivity of the classical oxidation of the double bond.

1. Experimental

General methods.—Solvents were freshly distilled prior to use and dried over molecular sieves. Evaporations were performed at reduced pressure. Column chromatography was carried out with Silica Gel 60 (E. Merck, 70–230 mesh), and TLC was carried out on precoated plates (E. Merck, 5724), with detection by charring with H_2SO_4 (10% in EtOH). Melting points were determined on a Büchi SMP-20 apparatus and are not corrected. Optical rotations were measured on a Jasco DIP-370 polarimeter in 1-dm tubes. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Brucker AC 400 spectrometer. Chemical shift data are given in ppm, and spin–spin coupling constants are in Hz. Elemental analyses were carried out by the Service Central d'Analyses du CNRS in Lyon, France.

General procedure for the synthesis of acrylidene acetals **1**, **4**, **7**, **10***[1]*.—To a solution of the sugar (0.01 mol) in 20 mL of anhyd DMF were added 1.5 mol equiv of acrolein diethylacetal and a catalytic amount of *p*-toluenesulfonic acid. The mixture was stirred at rt during 12 h, and the reaction was monitored by TLC (EtOAc). The reaction was quenched by addition of NEt_3, and the solvent was removed under reduced pressure. The residue was then acetylated under the usual conditions (Ac_2O–pyridine, 0 °C overnight). The usual workup afforded the attempted protected acetal, which was purified by silica-gel column chromatography.

Data for **1**: mp 79–81 °C, $[\alpha]_D^{20}$ +122° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 5.75 (m, 1 H, H-8), 5.45 (m, 2 H, H-3, 9), 5.25 (m, 1 H, H-9′), 4.95 (d, 1 H, H-7), 4.75 (m, 2 H, H-1, 2), 4.20 (m, 1 H, H-6), 3.75 (m, 1 H, H-6′), 3.60, 3.50 (2m, 2 H, H-4,5), 3.35 (s, 3 H, OMe), 2.05 (2s, 6 H, OAc). ^{13}C NMR ($CDCl_3$): δ 20.7–21.0 (OAc), 55.4 (OMe), 63.4–80.5 (C-2,3,4,5,6), 100.9, 99.9 (C-1,7), 119.6 (C-9), 133.4 (C-8), 169.8–170.3 (OAc). Anal. Calcd for $C_{14}H_8O_{20}$: C, 53.16; H, 6.33. Found: C, 52.96; H, 6.41; data for **4**: physical data are identical to those previously published.[1] ^{1}H NMR ($CDCl_3$): δ 5.70 (m, 1 H, H-8), 5.50 (d, 1 H, H-1), 5.35,

5.20 (2m, 5 H, H-3, 3′, 4′, 9, 9′), 4.85 (m, 1 H, H-7), 4.65 (m, 1 H, H-2), 4.10, 3.45 (2m, 9 H, H-1′a, 1′b, 4, 5, 5′, 6ab, 6′ab), 2.0 (m, 18 H, OAc). ^{13}C NMR ($CDCl_3$): δ 171.1–169.7 (OAc), 133.2 (C-8), 118.9 (C-9), 104.0–62.0 (C-2, 2′, 3, 3′, 4, 4′, 5, 5′, 6, 6′), 100.5, 88.7 (C-1, 7), 20.7–20.3 (OAc); data for **7**: mp 115–116 °C, $[\alpha]_D^{20}$ +158° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 5.75 (m, 1 H, H-8), 5.45 (m, 3 H, H-3, 3′,9a), 5.25 (m, 3 H, H-1, 1′, 9b), 4.95 (m, 4 H, H-2, 2′,4′, 7), 4.20 (m, 1 H, H-6′a), 4.00 (m, 3 H, H-5′, 6′b, 6a), 3.85 (m, 1 H, H-5), 3.50 (m, 2 H, H-4, 6b), 2.00 (m, 18 H, OAc). ^{13}C NMR ($CDCl_3$): δ 170.5–169.6 (OAc), 133.0 (C-8), 119.5 (C-9), 101.0 (C-7), 93.3, 92.2 (C-1, 1′), 78.6–60.3 (C-2–C-6, C-2′–C-6′), 20.8–20.6 (OAc). Anal. Calcd for $C_{27}H_{17}O_{36}$: C, 51.25; H, 5.70. Found: C, 50.71; H, 5.84; data for **10**: mp 175–177 °C, $[\alpha]_D^{20}$ +166° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 5.75 (m, 2 H, H-8, 8′), 5.45 (m, 4 H, H-3, 3′, 9a, 9′a), 5.25 (m, 4 H, H-1, 1′, 9b, 9′b), 4.90 (m, 4 H, H-2, 2′, 7, 7′), 4.00, 3.83, 3.50 (3 m, 8 H, H-4, 4′, 5, 5′, 6a, 6b, 6′a, 6′b), 2.05 (2s, 12 H, OAc). ^{13}C NMR ($CDCl_3$): δ 170.3–169.4 (OAc), 133.1 (C-8, 8′), 119.7 (C-9, 9′), 101.0 (C-7, 7′), 93.0 (C-1, 1′), 78.5-63.0 (C-2–C-6, C-2′–C-6′), 20.8–20.6 (OAc). Anal. Calcd for $C_{26}H_{15}O_{34}$: C, 53.24; H, 5.80. Found: C, 53.40; H, 5.96.

General procedure for oxidation with $PdCl_2$.—In a round-bottom flask were introduced successively 0.2 mol equiv of palladium chloride, 1 mol equiv of benzoquinone and a solution of the starting acetal in distilled DMF. The mixture was stirred under nitrogen at rt for 18–24 h. Water was added portionwise as follows: 1 mL at the beginning and additional quantities (1 mL) after 0.25, 0.5, 0.75 h. The total ratio of DMF–water was 9:1. The progress of the oxidation was monitored by TLC. When all the starting material had disappeared, the reaction was quenched with water. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with water and then dried. Removal of the solvent left a mixture that was purified by column chromatography (EtOAc–cyclohexane).

Data for **2**: yield 80%, $[\alpha]_D^{20}$ +132° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.65 (s, 1 H, H-9), 5.40 (m, 1 H, H-3), 5.00 (d, 1 H, H-7), 4.90 (d, 1 H, H-1), 4.80 (m, 1 H, H-2), 4.10 (m, 1 H, H-6), 3.75 (m, 1 H, H-6′), 3.55, 3.45 (2m, 2 H, H-4, 5), 3.35 (s, 3 H, OMe), 2.70 (m, 2 H, H-8, 8′), 2.05, 2.00 (2s, 6 H, OAc). ^{13}C NMR ($CDCl_3$): δ 198.5 (*C*HO), 170.3–169.2 (OAc), 99.6, 97.5 (C-1, 7), 77.4, 69.1, 68.7, 62.0 (C-2, 3, 4, 5), 55.4 (OMe), 47.6 (C-8), 20.7 (OAc); data for **3**: ^{1}H NMR ($CDCl_3$): δ 5.45, 4.80 (2m, 3 H, H-1, 2, 3), 4.65 (s, 1 H, H-7), 4.20, 3.80, 3.55, 3.45 (4m, 4 H, H-4, 5, 6, 6′), 3.35 (s, 3 H, OMe), 2.15 (s, 3 H, H-9, 9′, 9″), 2.05 (2s, 6 H, OAc). ^{13}C NMR ($CDCl_3$): δ 200.3 (C-8), 170.3–169.8 (OAc), 100.1, 99.5 (C-1, 7), 81.8–62.0 (C-2–C-5), 68.7 (C-6), 55.4 (OMe), 25.0 (C-9), 21.0–20.7 (OAc); data for **5**: yield 55%, $[\alpha]_D^{20}$ +43° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.70 (s, 1 H, H-9), 5.65 (d, 1 H, H-1), 5.40 (m, 3 H, H-3, 3′, 4), 5.00 (m, 1 H, H-7), 4.80 (m, 1 H, H-2), 4.20, 3.50 (2m, 9 H, H-1′a, 1′b, 4′, 5, 5′, 6a, 6b, 6′a, 6′b), 2.70 (m, 2 H, H-8, 8′), 2.10 (m, 18 H, OAc). ^{13}C NMR ($CDCl_3$): δ 198.3 (*C*HO), 170.5–169.6 (OAc), 104.0 (C-2′), 99.1, 90.3 (C-1, 7), 79.3-63.0 (C-2–C-5, C-2′–C-5′), 47.6 (C-8), 20.5–20.7 (OAc). Anal. Calcd for $C_{19}H_{20}O_9$: C, 50.0; H, 5.6. Found: C, 49.74; H, 5.78; data for **6**: ^{1}H NMR ($CDCl_3$): δ 5.60 (s, 1 H, H-1), 4.75 (m, 1 H, H-2), 4.60 (s, 1 H, H-7), 2.10 (s, 3 H, H-9a, 9b, 9c), 2.05–2.00 (m, 18 H, OAc); data for **8**: yield 80%, $[\alpha]_D^{20}$ +111° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 5.45 (m, 2 H, H-3, 3′), 5.30, 5.20 (2 m, 2 H, H-1, 1′), 4.95 (m, 4 H, H-2, 2′, 4′, 7), 3.80–4.20 (3m, 5 H, H-4, 5, 5′, 6′a, 6′b), 3.50 (m, 2 H, H-6a, 6b), 2.70 (m, 2 H, H-8a, 8b), 2.05 (m, 18 H, OAc). ^{13}C NMR ($CDCl_3$): δ 198.0 (*C*HO), 171.0–169.3 (OAc), 98.1 (C-7), 93.1, 92.1 (C-1, 1′), 79.0–60.2 (C-2–C-6, C-2′–C-6′), 47.5 (C-8), 20.4–20.5 (OAc). Anal. Calcd for $C_{27}H_{36}O_{18}$: C, 50.6; H, 6.0. Found: C, 50.19; H, 6.20; data for **9**: ^{1}H NMR ($CDCl_3$): δ 5.45 (m, 2 H, H-3, 3′), 5.30, 5.20 (2m, 2H, H-1, 1′), 4.95 (m, 3 H, H-2, 2′, 4), 4.60 (s, 1 H, H-7), 4.25–3.40 (4m, 7 H, H-4, 5, 5′, 6a, 6b, 6′a, 6′b), 2.15 (s, 3 H, H-9a, 9b, 9c), 2.10–1.90 (5s, 18 H, OAc); data for **11**: mp 102–104 °C, $[\alpha]_D^{20}$ +152° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.85 (s, 2 H, C*H*O), 5.50 (m, 2 H, H-2, 2′), 5.25 (d, 2 H, H-1,1′), 4.95 (d, 2 H, H-7, 7′), 4.85 (m, 2 H, H-3,3′), 4.10–3.50 (4m, 8 H, H-4, 4′, 5, 5′, 6a, b, 6′a, b), 2.65 (d, 4 H, H-8a, 8b, 8′a, 8′b), 2.02 (2 s, 12 H, OAc). ^{13}C NMR ($CDCl_3$): δ 198.1 (*C*HO), 170.1–169.6 (OAc), 98.2, 93.0 (C-7, 7′, 1, 1′), 78.9–62.8 (C-2–C-6, C-2′–C-6′), 47.6 (C-8, 8′), 20.7–20.4 (OAc); data for **12**: ^{1}H NMR ($CDCl_3$): δ 5.45, 5.20 (2m, 2 H, H-2, 2′, 3, 3′), 4.95, 4.85 (2m, 4 H, H-1, 1′, 7, 7′), 4.10–3.45 (4m, 8 H, H-4, 4′, 5, 5′, 6a, 6b, 6′a, 6′b), 2.15 (s, 3 H, H-9a, 9b, 9c), 2.10–2.00 (5s, 12 H, OAc).

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