The Knoevenagel-Doebner Reaction on 1,2-O-(2,2,2-Trichloroethylidene) Derivatives of D-Gluco- and D-Manno- f uranose †

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† Initial data was presented at the 11th International Electronic Conference on Synthetic Organic Chemistry, ECSOC-11, 1-30 November 2007, a007.

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Received: 8 October 2010; in revised form: 25 October 2010 / Accepted: 28 October 2010 / Published: 29 October 2010

Abstract: The synthesis of new α,β-unsaturated f uranuronic acid derivatives of α-gluco-(3), β-gluco- (6) and β-manno-chloraloses (9) via a convenient one pot procedure using the Knoevenagel-Doebner reaction approach are described. The dialdofuranose derivatives were reacted with malonic acid under Knoevenagel-Doebner reaction conditions and (E)-α,β-unsaturated f uranuronic acid derivatives were obtained.

Keywords: chloralose; trichloroethylidene; dialdofuranose; Knoevenagel-Doebner reaction; sugar chain extension

1. Introduction

In Organic Chemistry the well-known Knoevenagel reaction is defined by condensation of an aldehyde or ketone with compounds possessing active methylene groups such as malonic esters, or malononitrile to yield an α,β-unsaturated carboxylate products [1]. If the condensation reaction is set
up in the presence of catalytic amounts of piperidine in a basic organic solvent such as pyridine, it is called the “Doebner modification of Knoevenagel reaction” or the “Knoevenagel-Doebner reaction or condensation” [2,3]. A trans- or E-α,β-unsaturated carboxylic acid is obtained as a decarboxylation product when malonic acid is heated in pyridine [2,3]. These type of condensation reactions also have been used in carbohydrate chemistry in order to extend sugar chains [4-7].

The Knoevenagel reaction can afford different types of compounds, depending on the acidic or basic catalysis employed. The condensation of unprotected reducing sugars with 1,3-dicarbonylic compounds under acidic conditions was reported in 1956 by Gonzalez [8]. The ZnCl₂-catalyzed Knoevenagel reaction in alcoholic solvents has been used recently as the first step of the syntheses of a cytotoxic compound, of selective inhibitors of L-fucosidases of E- and P-selectin ligands, of glyco- and peptidomimetics, and of furan amino acid analogs of D- and L-serine. The so-called “Garcia Gonzalez reaction” was reinvestigated in order to improve yields using milder conditions such as CeCl₃, InCl₃, Sc(OTf)₃, FeCl₃, and scandium cation-exchanged montmorillonite [9].

The Knoevenagel condensation under basic conditions was first investigated with D-glucosamine chloride as the sugar. The reaction was extended to aldose and carbon nucleophiles such as barbituric acids and pentane-2,4-dione. When barbituric acids were used unprotected sugars gave C-glycosyl barbiturates. Reaction of pentoses or hexoses with Meldrum’s acid in DMF gave the unsaturated lactone. The condensation of pentane-2,4-dione with unprotected sugars in alkaline aqueous media was explored by the group of Lubineau. The condensation product of xylose with pentane-2,4-dione using NaOH, when reduced gave an activator of glycosaminoglycans biosynthesis used in cosmetic skincare products such as L’Oreal’s Pro-Xylane™ [9].

The aldehydo-derivatives of monosaccharides readily react with malonic acid in pyridine in the presence of piperidine catalyst [4]. The Knoevenagel-Doebner reaction of open-chain and protected monosaccharides is known in the literature [4,10-14]. For instance, 2,3-dehydro-2,3-dideoxyaladonic acids of starting monosaccharides were obtained via Knoevenagel-Doebner condensation of free L-arabinose, D-xylose and D-galactose with malonic acid [10]. Furthermore, the condensation products of protected monosaccharides such as aldehydo-1,2,3,4-di-O-isopropylidene-α-D-galacto-1,6-hexadialdo-1,5-pyranose [11] and 2,4-O-ethylidene-D-erythrose and threose [12] were reported.

Knoevenagel-Doebner syntheses have also been performed with the monomethyl ester of malonic acid and unsaturated chain-extended monosaccharide products were thus obtained. When 2,3-O-isopropylidene-D-glyceraldehyde and 2,3;4,5-di-O-isopropylidene-D-arabinose were used as a starting materials, methyl trans-2,3-dideoxy-4,5-O-isopropylidene-D-glycero-pent-2-enolate [13] and methyl trans-2,3-dideoxy-4,5;6,7-di-O-isopropylidene-D-arabin-o-hept-2-enolate [14] were formed, respectively, under very mild conditions.

Chloralose was firstly synthesized by Arthur Heffter in 1889 from the condensation of D-glucose and trichloroacetaldehyde (chloral) in the presence of an acid catalyst [15]. While two optical isomers were obtained α-glucocloralose (1) (α-chloralose) and β-glucocloralose (4) (β-chloralose) from the reaction of D-glucose with chloral, only β-isomers were obtained in the syntheses of β-xyloclohalrose [16] from D-xylose, β-arabinocloralose [17] from D-arabinose, β-galactochloralose [18] from D-galactose, β-mannochloralose (7) [19] from D-mannose via the same synthetic procedure.

Chloraloses are furanose-type cyclic acetals of pentoses and hexoses containing a 1,2-O-trichloroethyldene ring. Although, trichloroethylidene rings are highly stable under acidic and mildly basic
conditions [19], they are unstable in strong bases such as a potassium tert-butoxide. The HCl elimination from trichloroethylidene ring of a chlora lose with a strong base such as alkoxides gives a cyclic ketene acetal [17,19,20]. The trichloroethylidene group can be removed by hydrogenation with Raney nickel followed by acidic hydrolysis [21].

Trichloroethylidene acetals such as α-chloralose (1) [(R)-1,2-O-(2,2,2-trichloroethylidene)-α-D-glucofuranose] are potential biologically active compounds [22]. α-Chloralose was used in humans till the early part of the twentieth century [23]. Recently, it has been widely used as a bird repellent, a rodenticide, and in neuroscience and veterinary medicine as an anesthetic and sedative [22-25]. It has been characterized as a molecule which has potent central nervous system activity and evaluated in human and animal models for its therapeutic properties [26,27]. It is an anesthetic that exerts minimal cardiovascular depression, little change in blood pressure and no change or only a small reduction in heart rate, thus it is widely used in animals [28].

In addition to the well-known effects of chloraloses, arabinochloralose has been used as an intermediate compound for the development of new antituberculosis drugs in pharmaceutical research [29]. Spiro-endoperoxide chloraloses [30,31] and aminochloraloses [32] were synthesized and investigated antimicrobial activity against some microorganisms.

2. Results and Discussion

α,β-Unsaturated carboxylic acid-containing sugar derivatives 3, 6, and 9 were synthesized from compounds 1, 4, and 7, respectively, as shown in Scheme 1. The structure of the Knoevenagel-Doebner condensation products 3, 6, and 9 was confirmed by using spectral methods (FTIR, 1H- and 13C-NMR). In the FT-IR spectrum of the new dialdoxofuranose compound 8, the bands corresponding to the –OH and C=O are observed at 3,493 cm\(^{-1}\) and 1,737 cm\(^{-1}\), respectively. The aldehyde proton of this compound appeared as a singlet at 9.65 ppm in the 1H-NMR spectrum, and the carbonyl group peak appeared at 201.8 ppm in the 13C-NMR spectrum.

In the IR spectra of compounds 3, 6, and 9 a broad OH absorption (stretching) band at 3,218, 3,453 and 3,446 cm\(^{-1}\), typical C=O absorption bands at 1,718, 1,702 and 1,693 cm\(^{-1}\) and characteristic C=C bands at 1,662, 1,668 and 1,658 cm\(^{-1}\) appeared, respectively. The –OH stretching bands of the carboxylic acid moieties were displayed at 3,481, 3,453 and 3,537 cm\(^{-1}\).

The 1H-NMR and 13C-NMR spectral data of compounds 3, 6, and 9 are listed in Table 1. The hydroxyl and carboxylic acid group protons appeared as singlets at 5.48, 5.55, 5.76 ppm and 12.32, 12.42, 12.50 ppm, respectively. The large coupling constants (15.6 to 16.0 Hz) between 5-H and 6-H prove the formation of the E-isomer [33].

Long range couplings (1.2 to 2.0 Hz) were observed between H-4 and H-6 of the Doebner products. For compound 3, this finding was previously explained as a result of a twisted conformation of the furanose ring causing the endo-trichloromethyl group to approach the 4-H hydrogen hence shifting it downfield [20,21].
Scheme 1. (a) NaIO₄ in MeOH-H₂O; (b) i. CH₂(COOH)₂ in piperidine cat. in pyridine at 60 °C, ii. 6 N HCl.

Table 1. The ¹H-NMR (400 MHz) chemical shifts (δ ppm) and J_H,H values (Hz) of Knoevenagel-Doebner condensation products of chloraloses.

| Comp. | 1-H  | H_A | 2-H | 3-H | 4-H | 5-H | 6-H | 7-H | OH   |
|-------|------|-----|-----|-----|-----|-----|-----|-----|------|
| 3     | 6.10 d, J₁₂= 3.9 Hz | 5.43 s | 4.68 d | 4.23 d, J₃₄= 3.1 Hz | 5.00 ddd, J₄₅= 5.5 Hz, J₆₈= 2.0 Hz | 6.75 dd, J₆₈= 15.6 Hz | 5.98 dd | 12.32 | 5.48 s |
| 6     | 6.28 d, J₁₂= 3.6 Hz | 5.85 s | 4.75 d | 4.19 bs | 4.76 m | 6.75 dd, J₆₈= 15.8 Hz, J₄₅= 5.6 Hz | 5.98 dd, J₆₈= 1.2 Hz | 12.42 | 5.55 |
| 9     | 6.14 d, J₁₂= 3.6 Hz | 5.92 s | 4.39 dd, J₃₄= 3.6 Hz | 4.84 dd, J₄₅= 4.4 Hz | 3.73 m | 6.75 dd, J₆₈= 5.6 Hz, J₄₅= 1.6 Hz | 5.99 dd | 12.50 | 5.76 |

The ¹³C-NMR spectra of compounds 3, 6, and 9 are also consistent with the proposed structures, exhibiting two double bond carbon signals (123.3-141.9; 142.2-124.5; 143.7-123.8 ppm) and a carbonyl carbon signal (168.1, 167.2, 167.2 ppm) (Table 2). The positive ion mode APCI-MS analysis of compound 3 gave molecular ion peaks at m/z 317/319/321 (18 %) (3 × chlorine isotopic pattern), 353/355/357/359 [[M + H]⁺ + Cl], 100 %, (4 × chlorine isotopic pattern), as the base peak groups.

Table 2. The ¹³C-NMR (100 MHz) chemical shifts (δ ppm) of Knoevenagel-Doebner condensation products of chloraloses.

| Comp. | COOH  | 5-C, 6-C | 1-C, CHCl₃ | CCl₃ | 2-C, 3-C, 4-C |
|-------|-------|----------|-----------|-----|-------------|
| 3     | 168.1 | 141.9, 123.3 | 107.1, 105.9 | 97.2 | 87.8, 81.8, 75.4 |
| 6     | 167.2 | 142.2, 124.5 | 108.7, 106.6 | 100.4 | 88.2, 81.1, 75.7 |
| 9     | 167.2 | 143.7, 123.8 | 109.4, 105.6 | 100.4 | 82.3, 79.0, 75.9 |

A two pot alternative synthesis of similar compounds has been reported previously [27,31,33]. Hence, now we report synthesis of α,β-unsaturated furanuronic acid derivatives via a more facile one
pot procedure using the Knoevenagel-Doebner reaction approach. This study is the first report of the synthesis of \((E)-\alpha,\beta\)-unsaturated furanuronic acid derivatives of \(\alpha\)-gluco-, \(\beta\)-gluco- and \(\beta\)-manno- chloralose.

3. Experimental

3.1. General

Melting points were measured with a Gallenkamp electrothermal melting point apparatus in capillary tubes and are uncorrected. \(^1\)H-NMR (400 MHz) and \(^13\)C-NMR (100 MHz) spectra were recorded on a Varian AS 400 NMR spectrometer. APCI positive polarity (30 eV) mass spectra were recorded on Agilent 1100 (LC-MSD) mass spectrometer. IR spectra were recorded on Perkin Elmer Spectrum 100 FTIR Spectrometer. Optical rotation measurements were carried out on an Rudolph Research Analytical Autopol II digital polarimeter. TLC and column chromatography were performed on precoated aluminium plates (Merck 5554) and silica gel 60 (Merck 7734), respectively. All solvent removals were carried out under reduced pressure. Compound 1 was commercially available from Sigma-Aldrich Corp. and contained 4 as an impurity. Compound 4 is soluble in cold methanol, but 1 is not, and thus, impurities of 4 in the crude 1 were removed with cold methanol. Compound 4 was purchased from Sigma-Aldrich Corp. and purified via crystallization from boiling methanol. Syntheses of \((R)-1,2-O-(2,2,2\text{-}trichloroethylidene)\-\(\alpha\)\-D\-xylo-1,4-furanodialdose (2) from 1, \((S)-1,2-O-(2,2,2\text{-}trichloroethylidene)\-\(\alpha\)\-D\-xylo-1,4-furanodialdose (5) from compound 4 were performed according to the literature via periodate oxidation reaction [31,33]. Compound 7 was synthesized from D-mannose and chloral according to the literature procedure [19].

5,6-Dideoxy-(R)-1,2-O-(2,2,2-trichloroethylidene)-\(\alpha\)-D-xylo-hept-5-(E)-eno-1,4-furanuronic acid (3). A solution of compound 2 (7.00 g, 0.024 mol) in pyridine (50 mL) was mixed with malonic acid (12.48 g, 0.12 mol) and piperidine (0.5 mL). The solution was stirred at 60 °C for 30 minutes and completion of the reaction was monitored with TLC (toluene/MeOH, 8:2). The reaction mixture was poured into a 1:1 H\(_2\)O/HCl solution (200 mL). The acidic solution was extracted with CH\(_2\)Cl\(_2\) (3 × 100 mL). Then the organic phase was dried with Na\(_2\)SO\(_4\) and solvent was removed under reduced pressure. The residue was purified via column chromatography on silica gel using CH\(_2\)Cl\(_2\):CH\(_3\)OH (95:5) as an eluent. Compound 3 was obtained as a white solid after recrystallisation from CH\(_2\)Cl\(_2\). (3.25 g, 42%); m.p. 150-151 °C; \([\alpha]\)_D\(^{22}\) : -77.9 (c 0.51 in CH\(_3\)OH); IR cm\(^{-1}\) (KBr): 3,481 (-COOH), 3,218 (-OH), 1,718 (C=O), 1,662 (C=C); \(^1\)H-NMR \(\delta\) (CDCl\(_3\)): 7-H 12.32 (s, 1H), 5-H 6.75 (dd, 1H, \(J_{5,6} = 15.6\) Hz), 1-H 6.10 (d, 1H, \(J_{1,2} = 3.9\) Hz), 6-H 5.98 (dd, 1H), OH 5.48 (s, 1H), HA 5.43 (s, 1H), 2-H 4.68 (d, 1H), 3-H 4.23 (d, 1H, \(J_{3,4} = 3.1\) Hz), 4-H 5.00 (ddd, 1H, \(J_{4,5} = 5.5\) Hz); \(^13\)C-NMR \(\delta\) (CDCl\(_3\)): 168.1 (COOH), 141.9, 123.3 (5-C, 6-C), 107.8, 105.9 (1-C, CHCl\(_3\)), 97.2 (C\(_{\text{Cl3}}\)), 87.8, 81.8, 75.4 (2-C, 3-C, 4-C); MS \(m/z\) 318 [M + H]\(^+\), 18 %, 317/319/321 (3 × chlorine isotopic pattern), 353/355/357/359 [M + H]\(^+\) + Cl], 100 %, (4 x chlorine isotopic pattern). Anal. Caled. for C\(_9\)H\(_9\)Cl\(_3\)O\(_6\): C, 33.83; H, 2.84. Found: C, 33.92; H, 2.83.
5,6-Dideoxy-(S)-1,2-O-(2,2,2-trichloroethylidene)-α-D-xylo-hept-5-(E)-eno-1,4-furanuronic acid (6). 
Synthesized from 5 (1 g, 3.60 mmol) by the same procedure described for 3. White solid, yield: 0.725 g (63%); m.p. 210-212 °C (dec.); [α]_D^26 -290.7 (c 0.86 in CH₃OH); IR cm⁻¹ (KBr): 3,453 (-OH and -COOH), 1,702 (C=O), 1,668 (C=C); ¹H-NMR δ (DMSO-d₆): 7-H 12.42 (bs, 1H), 5-H 6.75 (dd, 1H, \(J_{4,5} = 5.6\) Hz, \(J_{5,6} = 15.8\) Hz), 1-H 6.28 (d, 1H, \(J_{1,2} = 3.6\) Hz), 6-H 5.98 (dd, 1H, \(J_{4,6} = 1.2\) Hz), H₆ 5.85 (s, 1H), OH 5.55 (bs, 1H), 4-H 4.76 (m, 1H), 2-H 4.75 (d, 1H), 3-H 4.19 (bs, 1H); ¹³C-NMR δ (DMSO-d₆): 167.2 (COOH), 143.8, 123.8 (5-C, 6-C), 109.4, 105.9 (1-C, CHCl₃), 100.4 (CHCl₃), 82.3, 79.0, 75.9 (2-C, 3-C, 4-C); Anal. Calcd. for C₉H₉Cl₃O₆: C, 33.83; H, 2.84. Found: C, 33.07; H, 2.52.

(R)-1,2-O-(2,2,2-trichloroethylidene)-β-D-lyxo-1,4-furanodialdose (8). The 1,4-furanodialdose derivative were synthesized according to previous literature [19]. A solution of compound 7 (5.00 g, 16.15 mmol) in methanol (160 mL) was mixed with an aqueous solution of NaIO₄ (4.02 g, 19.23 mmol). TLC analysis showed that the synthesis of (R)-1,2-O-(2,2,2-trichloroethylidene)-β-D-lyxo-1,4-furanodialdose was completed in 3.5 hours at room temperature. Reaction mixture was filtered, the filtrate was concentrated under reduced pressure and extracted with CH₂Cl₂ (4 × 150 mL). The organic phase was dried over anhydrous Na₂SO₄ and then evaporated to afford dialdofuranose 8 (3.55 g, 79 %) as a pure white amorphous powder, m.p. 115-117 °C (dec.); [α]_D^26: 0.11 (c 0.17 in CH₃OH); IR cm⁻¹ (KBr): 3,493 (-OH), 1,737 (C=O); ¹H-NMR δ (DMSO-d₆): 5-H 9.65 (s, 1H), 1-H 6.13 (d, 1H, \(J_{1,2} = 3.6\) Hz), H₆ 5.54 (s, 1H), OH 6.10 (bs, 1H), 2-H 4.81 (dd, 1H, \(J_{2,3} = 3.6\) Hz), 3-H and 4-H 4.60 (m, 2H). ¹³C-NMR δ (DMSO-d₆): 201.8 (CHO), 109.4, 106.6 (1-C, CHCl₃), 101.0 (CHCl₃), 84.1, 82.2, 73.9 (2-C, 3-C, 4-C); Anal. Calcd. for C₇H₇Cl₃O₅: C, 30.30; H, 2.54. Found: C, 29.83; H, 2.27.

5,6-Dideoxy-(R)-1,2-O-(2,2,2-trichloroethylidene)-β-D-lyxo-hept-5-(E)-eno-1,4-furanuronic acid (9). 
Synthesized from 8 (1 g, 3.60 mmol) by the same procedure described for 3. White solid, yield: 0.83 g (72 %); m.p. 195-197 °C; [α]_D^26: -171.6 (c 1.02 in CH₃OH); IR cm⁻¹ (KBr): 3,537 and 3,446 (-OH and -COOH), 1,693 (C=O), 1,658 (C=C); ¹H-NMR δ (DMSO-d₆): 7-H 12.50 (s, 1H), 5-H 6.75 (dd, 1H, \(J_{4,5} = 5.6\) Hz, \(J_{5,6} = 16.0\) Hz), 1-H 6.14 (d, 1H, \(J_{1,2} = 3.6\) Hz), 6-H 5.99 (dd, 1H, \(J_{4,6} = 1.6\) Hz), H₆ 5.92 (s, 1H), OH 5.76 (bs, 1H), 4-H 4.84 (dd, 1H, \(J_{3,4} = 4.4\) Hz), 2-H 4.39 (dd, 1H, \(J_{2,3} = 3.6\) Hz), 4-H 3.73 (m, 1H); ¹³C-NMR δ (DMSO-d₆): 167.2 (COOH), 143.7, 123.8 (5-C, 6-C), 109.4, 105.6 (1-C, CHCl₃), 100.4 (CHCl₃), 82.3, 79.0, 75.9 (2-C, 3-C, 4-C); Anal. Calcd. for C₉H₉Cl₃O₆: C, 33.83; H, 2.84. Found: C, 33.20; H, 2.54.

4. Conclusions
In the present work, the one-pot synthesis of three new potentially biological active furanuronic acid derivatives based on the 1,2-O-(2,2,2-trichloroethylidene) unit from via a Knoevenagel-Doebner reaction of the corresponding trichloroethylidene pentadialdofuranose was achieved. The spectroscopic data of the condensation products indicate the formation of only E-isomers of the carbon-carbon double bonds.
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*Sample Availability:* Samples of the compounds are available from the authors.

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