[a007]

KNOEVENAGEL CONDENSATION OF *α*-CHLORALOSE DERIVATIVE

Gökhan KÖK[b], Tamer KARAYILDIRIM[b], Kadir Ay[a], Emriye AY[a]

Email: emriye.ay@bayar.edu.tr

[a] Celal Bayar University, Faculty of Art and Sciences, Chemistry Department, Manisa 45030, Turkey.
[b] Ege University, Faculty of Science, Chemistry Department, Bornova, İzmir 35100, Turkey.

Abstract – *α*-chloralose derivative aldehyde reacted with malonic acid via Knoevenagel condensation. The structure of *α,β*-unsaturated carboxylic acid product was characterized with spectroscopic methods.

Keywords: Knoevenagel condensation; Unsaturated sugar; chloralose.

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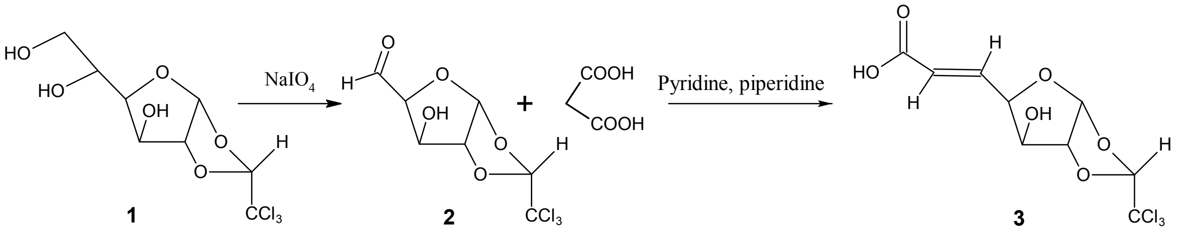
1. Introduction

Knoevenagel condensation is a well-known reaction of organic chemistry but not widespread in carbohydrate chemistry. Generally, this condensation is made by the reaction of an aldehyde with malonic acid or derivatives in the presence of piperidine catalyst in pyridine. The product is only *trans*-*α,β*-unsaturated carboxylic acid or derivative.

Trichloroethylidene acetals are useful protecting groups since they are highly stable in acid media, thus, allowing acid catalysed reactions to be carried out on parent compounds. Their removal is possible by hydrogenation with Raney nickel followed by acid hydrolysis. They can be converted to dichloroethylidene ketene acetals or to dichloroacetyl orthoesters by their reaction with potassium *t*-butoxide. Dichloroacetyl orthoesters have found use as donors in the formation of glycosides. Trichloroethylidene acetals are potentially biologically active compounds; *α*-chloralose (1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose) is a hypnotic which is used as an animal anaesthetic[1,2,3].

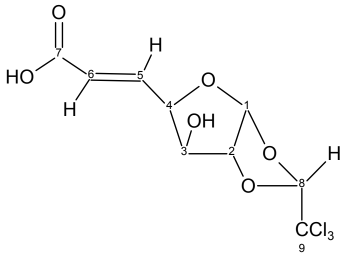
2. Results And Discussion

α,β-Unsaturated carboxylic acid containing derivative of *α*-chloralose has been synthesized from *α*-chloralose as figured in following reactions:



Structure has been confirmed by using spectral methods (FTIR-, ^{1}H-NMR-, ^{13}C-NMR- and mass spectra).

In FTIR-spectrum (**Figure 1**) of 5,6-dideoxy-(*R*)-1,2-*O*-trichloroethylidene-*α*-D-*xylo*-hept-5-(*E*)-eno-1,4-furanouronic acid there were absorption bands in region 3219 cm^{-1}, characterizing for stretching vibrations of OH-alcohol groups in carbohydrate part. Carboxylic acid OH group has an absorption band in region 3481cm^{-1} and C=O bond has an absorption band in region 1718 cm^{-1}.The C=C bond have been characterized by some absorption bands in regions 1662 cm^{-1}



^{1}H-NMR and ^{13}C-NMR (**Figure 2 and 3**) spectral data of compound **3** are shown in **Table 1**. The protons of hydroxyl group is and carboxylic acid specified by broadsinglet chemical shifts at 5.48 ppm and the proton of carboxylic acid is specified 12.32 ppm. High coupling (15.6 Hz) between H-5 and H-6 is proof of *E*-isomer structure. This finding was previously explained as a result of a twisted conformation of the furanose ring causing the *endo*-trichloromethyl group to approach the H-4 hydrogen hence shifting it downfield[4].

^{13}C NMR spectrum is also consistent with the proposed structure, exhibiting two double bond carbons (123.29-141.88 ppm) and carbonyl carbon (168.12 ppm).

Positive polarity APCI MS spectrum in methanol–chloroform produced (M+1) peaks at m/z 317/319/321 (18%) (3 x chlorine isotopic pattern), 353/355/357/359 [(M+1)+Cl], 100%, (4 x chlorine isotopic pattern), as the base peak group.

Table 1. 1H and 13C NMR spectral data of compound **3**

Location of atoms	**^{1}H NMR (δ)**	**H and J couplings (Hz)**	**^{13}C NMR (δ)**
H-7	12.32 s	1 H	168.12
H-5	6.75 dd	1 H, $J_{4,5}$= 5.5, $J_{5,6}$=15.6	141.88, 123.29
H-6	5.98 dd	1 H, $J_{4,6}$= 2.0	
H-1	6.10 d	1 H, $J_{1,2}$= 3.9	107.07, 105.94, 97.19 (CCl_3)
HA	5.43 s	1 H	
H-4	5.00 ddd	1 H	87.77, 81.75, 75.36
H-2	4.68 d	1 H	
H-3	4.23 d	1 H, $J_{3,4}$= 3.1	
OH	5.48 s	1 H	

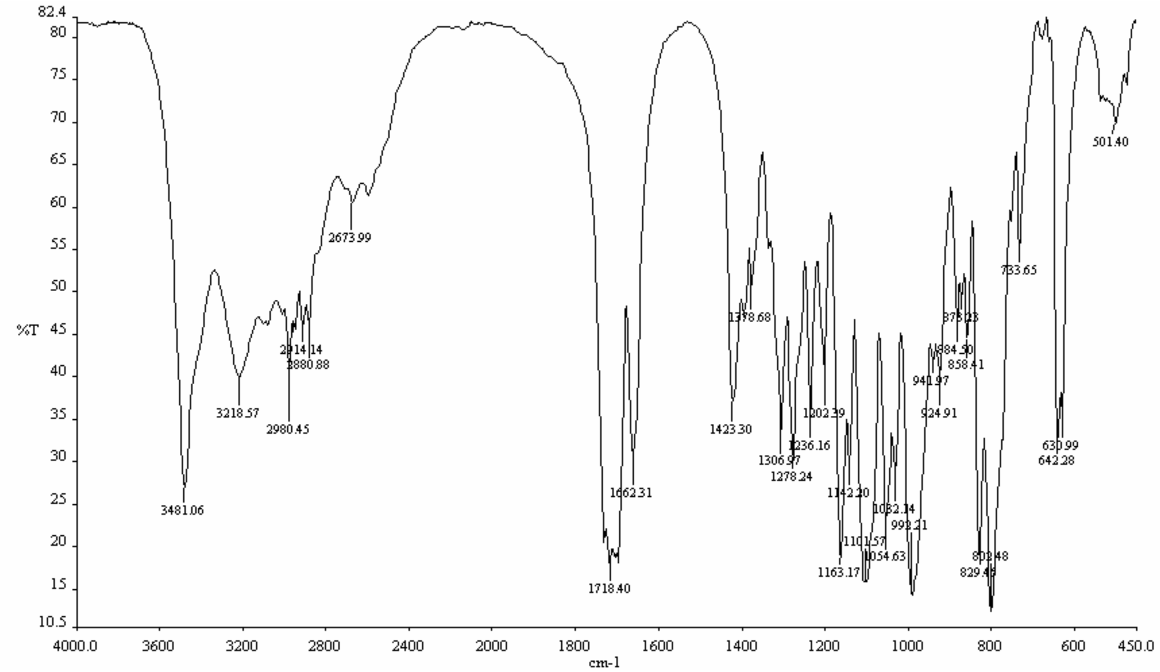


Figure 1. FTIR spectrum of the compound **3** in KBr

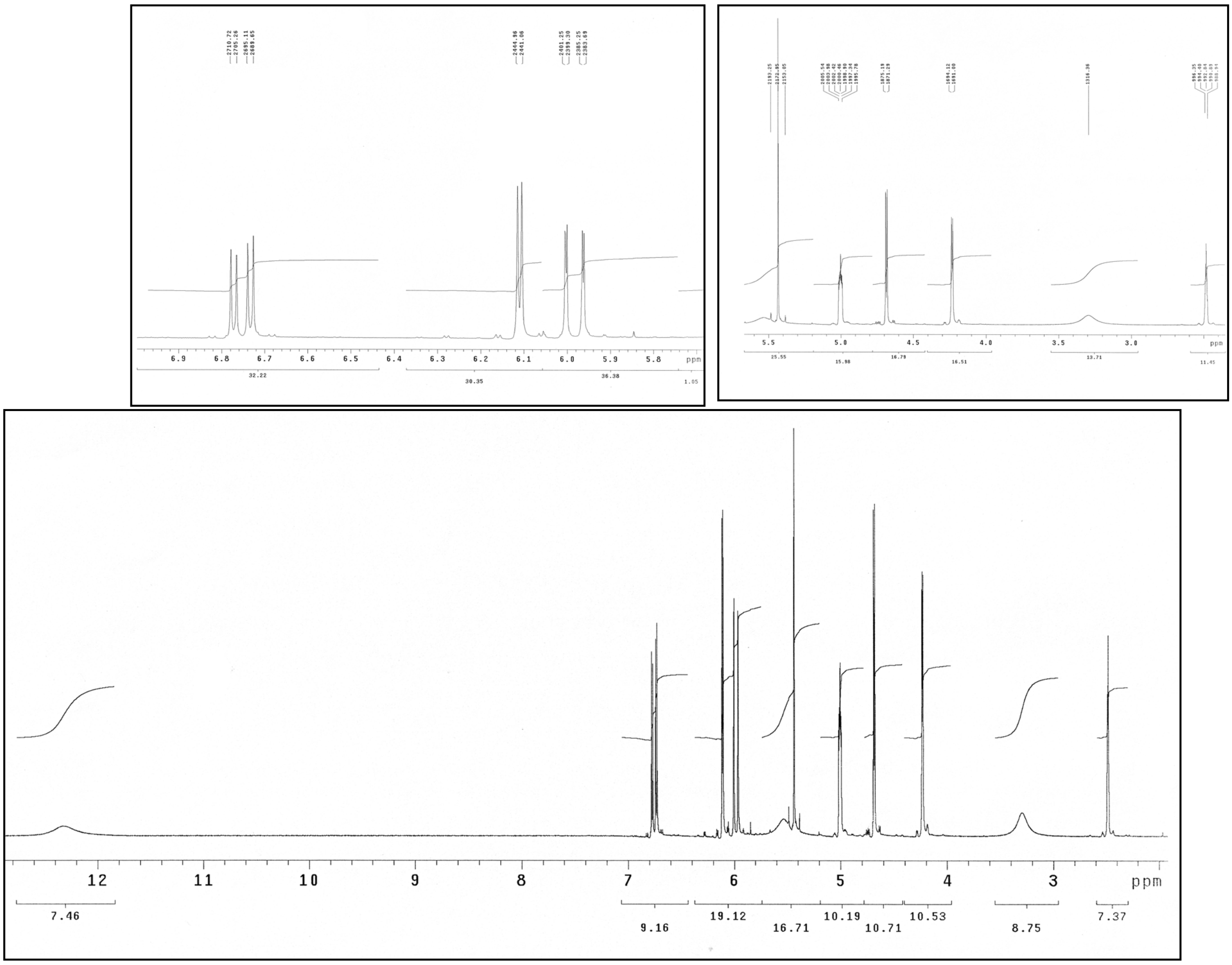


Figure 2. ^{1}H NMR spectrum of the compound **3** in DMSO-d6

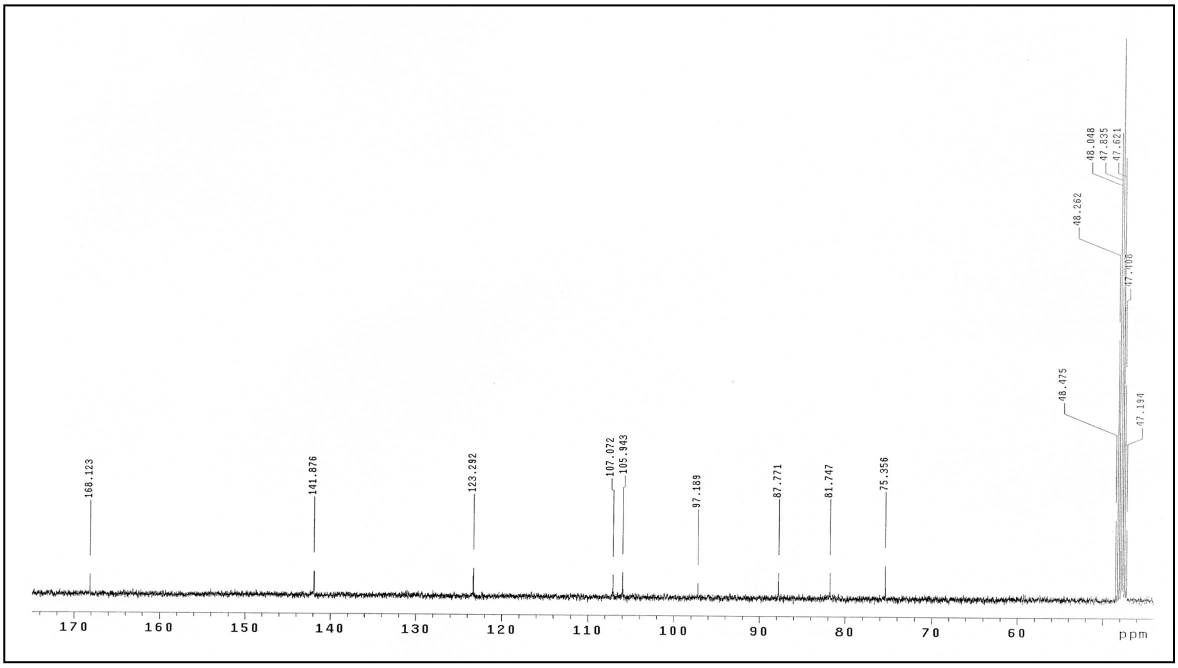
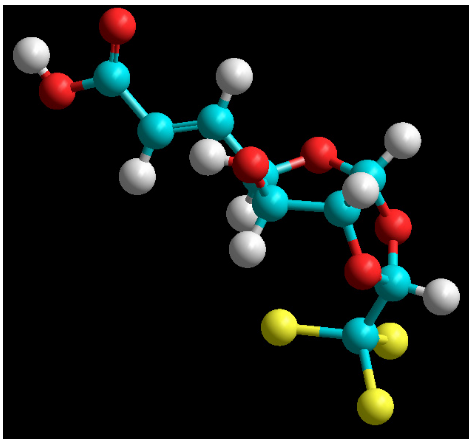


Figure 3. ^{13}C NMR spectrum of the compound **3** in CD_3OD

Molecular modelling calculations were perfomed on HyperChem Release 7.5 software and calculation method was Semi-emprical method PM3. The optimized molecular structure was shown as following figure.



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3. Experimental Part

Melting points were measured by using Gallenkamp electrotermal melting point apparatus in capillary and uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Varian AS 400 NMR spectrometer. APCI positive polarity (30eV) 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 a Schimidt-Haensch Polartronic E polarimeter. TLC and column chromatography were performed on precoated aluminium plates (Merck 5554) and silica gel G-60 (Merck 7734), respectively. All solvent removals were carried out under reduced pressure.

3.1. *1,2-O-(R)-Trichloroethylidene-α-D-xylo-1,4-furanodialdose*[1] (**2**)

Commercial *α*-chloralose (1) containing *β*-chloralose soluble in cold methanol but *β*-chloralose insoluble. *α*-chloralose purified in cold methanol and solvent was removed under reduced pressure. Periodate oxidation of (*R*)-1,2-*O*-trichloroethylidene-*α*-D-glucofuranose (*α*-chloralose) was made according to literature[1].

A hot solution of *α*-chloralose (10 g, 0.33 mol) in CH_3OH (150 mL) was mixed with a solution of $NaIO_4$ (8 g, 0.038 mol) in H_2O (200 mL) and stirred until a clear solution gained. The solution was allowed to stand at room temperature for 4 h. The mass of crystals which formed was filtered and washed with CH_3OH. The filtrate and the washings were combined and concentrated under reduced pressure to give a solid product. The solid was extracted with CH_2Cl_2 and evaporated under reduced pressure. The syrupy product solidified in air over night. White solid, 3.2 g (65 %), mp 139°-142 °C (decomp.) (lit. mp 138°-142 °C decomp.).

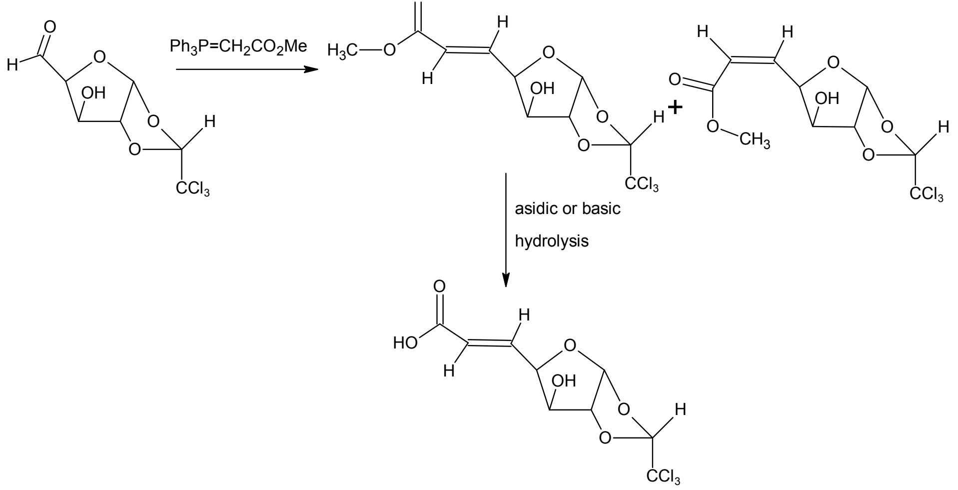
3.2. *5,6-Dideoxy-(R)-1,2-O-trichloroethylidene-α-D-xylo-hept-5-(E)-eno-1,4-furanouronic acid* (**3**)

A solution of compound 2 (7 g, 0.024 mol) in pyridine (50 mL) was mixed with malonic acid (12.48g, 0.12 mol) and piperidine (0.5 mL) and stirred. The solution was allowed to stand at 100 °C for 6 h. The mixture was poured in H_2O-HCl (200 mL 1:1) solution. The asidic solution was extracted with 3x100 mL CH_2Cl_2 . The organic phase was dried with Na_2SO_4. The solvent was removed under reduced pressure. The solid applied to a silicagel column with (CH_2Cl_2-CH_3OH, 95:5). Fractions (5 mL) were collected and examined with TLC (Tol-Me, 8:2). Fractions containing the product were combined and evaporated to give a white solid and recrystallized from CH_2Cl_2. White solid, 3.25 g (42%), mp 150-151 ^{o}C, $[\alpha]_{D}^{22}$ -77.90 (*c* 0.514, CH_3OH). MS *m/z* 318 (M+1), 18%, 317/319/321 (3 x chlorine isotopic pattern), 353/355/357/359 [(M+1)+Cl], 100%, (4 x chlorine isotopic pattern). Anal. Calcd for $C_9H_9Cl_3O_6$: C, 33.83; H, 2.84. Found: C, 33.92; H, 2.83.

4. Conclusion

5,6-dideoxy-(*R*)-1,2-*O*-trichloroethylidene-*α*-D-*xylo*-hept-5-(E)-eno-1,4-furanouronic acid has been synthesized from *α*-chloralose. It's structure has been confirmed using modern spectroscopic methods.

In two pot alternative synthesis of this product, firstly aldehyde was reacted with Ph_3P=CH_2CO_2Me. *E*- and *Z*-Wittig products were seperated using with silica gel chromatgraphy. Secondly, *E*-Wittig product was hydrolyzed in asidic or basic media. But Knoevenagel reaction is one pot.



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