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Thermal and Crystallographic Characteristics of Synthesized Xanthen-3-one Derivatives

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Abstract: Series of synthesized xanthen-3-one derivatives were analyzed for thermal characteristics by differential scanning calorimetry (DSC), as well as for crystallinity using X-ray powder diffraction. Xanthen-3-one derivatives are prepared according to the well known procedure, which includes two-fold Friedel-Crafts alkylation. The aim of this research was to determine purity and crystallinity of synthesized xanthen-3-one derivatives.

Thermograms of synthesized compounds showed that compounds have purity above 98%, while crystallographic analysis of powder showed that the compounds have a 10-37% monocrystalline form.

INTRODUCTION

Studies of natural and synthetic xanthones and its derivatives have been present for a number of years. Derivatives of xanthone are characterized by excellent chemical reactivity and different bioactivity. Their remarkable biological potential is the reason for synthesis of many new products, suitable for application in modern therapy.[1]

Over recent years, there was increased interest in these compounds because of their important biological activities, such as inhibition of monoamine oxidase (MAO) enzymes, antiprotosoal[2], antioxidant[3,4], antiulcer, bronchodilatation action and it is also used *in vivo* and *in vitro* as antitumoral agents.[5-7]

Natural xanthones are highly biologically active, possess anti-inflammatory properties such as COX inhibition and have cardiovascular protective effects.[8]

Also, recent studies have shown that xanthene derivatives have cardioprotective effect acting as antiarrhythmics.[9]

In addition, we discuss the synthesis of novel xanthene-3-on derivatives and their thermal behavior and crystallinity.

EXPERIMENTAL

General procedure for the preparation of xanthen-3-one derivatives

A round-bottomed flask equipped with a condenser and mechanical stirrer was filled with 1,2,4-triacetoxybenzene (5 g) in 50% EtOH (75 mL). Conc. sulfuric acid (3 mL) was added and the white suspension was heated to reflux, resulting in a clear, honey colored solution. To this mixture various benzaldehydes (10 mmol) were added dropwise within 2 min. The stirred mixture was kept at reflux for another 60 min. Subsequently, potassium peroxodisulphate (2.70 g) was added at 80°C within a period of 50 min in small portions. The contents were brought to reflux for another 20 min and then poured onto ice water. Obtained red fluorescent crystals were washed with cold water and after drying in vacuum at 60°C crystallized from glacial acetic acid or from ethanol.

General procedures for analytical and experimental section

Microanalyses for C, H and N were preformed on Perkin Elmer 2400 elementary analyzer (Germany). IR spectra were recorded on Perkin Elmer FT-IR 1000 (Germany) in KBr discs. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300,075 MHz, in DMSO-*d*6, on NMR Spectrometer, Varian Unity Plus 500 MHz and Bruker Advance DPX 300 MHz (Varian, UK). Thermal characteristics of synthesized compounds were determined by differential scanning calorimetry (DSC) using a Perkin Elmer Pyris Diamond DSC calorimeter, at heating rate of 10˚C/min with a sample volume of 2 mg. Scanning was performed by heating the sample for 1 min at 50°C, and then in the temperature range 50-300°C.

Differential scanning calorimetry (DSC) may be used as simple and rapid method of estimating the purity of compounds. The method is based on the van't Hoff law of melting point depression expressed as:

$$T_0 - T_m = (RT_0^2X_2/\Delta H_f) \cdot (1/F) \quad (1)$$

Crystallinity of compounds was examined by X-ray powder diffraction (XRPD) using a Philips PW 1730/10 diffractometer with a graphite-monochromatized Cu $K\alpha_1\alpha_2$ radiation [$\lambda(K\alpha_1)$ = 1.54056 Å, $\lambda(K\alpha_2)$ = 1.54439 Å]. X-ray diffraction patterns were recorded in steps of 0.02° (2θ) in the 2θ range from 5° to 100° with a fix counting time of 1 s per step. Determination of the crystallinity level for the samples was performed with the program X'Pert HighScore Plus, version 2.1.[11] according to equation:

$$Crystallinity[\%] = 100 \cdot \frac{\sum I_{net}}{(\sum I_{tot} - Bgr._{const.})} \quad (2)$$

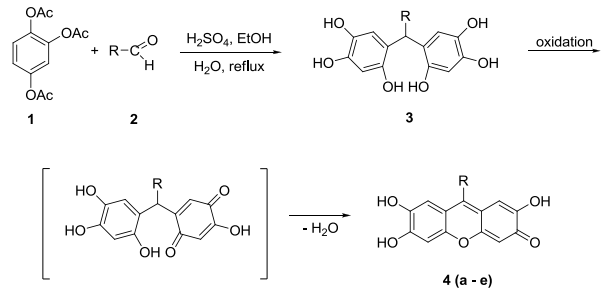
where I_{net} is diffracted intensity from the crystalline part of sample, I_{tot} is complete measured intensity from the sample (both, intensity of X-ray diffraction from the crystalline part of sample and intensity of X-ray scattering from the amorphous part of sample). $Bgr._{const.}$ is a constant background intensity determined for the crystalline standard. The summation is taken over measured 2θ steps in the whole measured range of Bragg angle.

RESULTS AND DISCUSSION

Chemistry

Novel derivatives of xanthene-3-ones have been prepared according the procedure described by Liebermann and Linndenbau[10,11], which includes two-fold Friedel-Crafts alkylation of 1,2,4-triacetoxybenzene (**1**), reflux in ethanol and sulphuric acid with addition of potassium peroxodisulphate as an oxidizing agent. The oxidation of **3** occurs under aerobic conditions over an extended period of time and by dehydratation afford xanthene-3-one derivatives (**4a** - **4e**), (Scheme 1).

The composition of the synthesized compounds was confirmed by elemental analysis, and structure of synthesized compounds was confirmed by spectroscopic methods: infrared spectroscopy (IR spectroscopy), proton nuclear magnetic resonance (^{1}H-NMR) and carbon nuclear magnetic resonance (^{13}C-NMR).



	R
4a	C_6H_5-
4b	o-OCH_3-C_6H_4-
4c	p-OCH_3-C_6H_4-
4d	o-Cl-C_6H_4-
4e	p-Cl-C_6H_4-

Scheme 1. Synthetic pathway for the preparation of xanthen-3-one derivatives.

9-Phenyl-2,6,7-trihydroxyxanthen-3-one (4a). Yield= 60.28%**.** Anal. calcd for $C_{19}H_{12}O_5$: C 71.40, H 3.45. Found: C 71.25, H 3.50. All values are given in percentages. IR (KBr) n 3600 2400 1590 1300 1200 690 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*6) d 7.8 (m, 2H, H-12 and H-16), 7.5 (m, 2H, H-13 and H-15), 7.2 (m, 1H, H-14), 6.8 (s, 2H, H-1 and H-8), 6.5 (s, 2H, H-4 and H-5).^{13}C NMR (150MHz, DMSO-*d*6) d 177.5 (C-3, C-6), 172 (C-3), 152.17 (C-2, C-7), 151.77 (C-4a, C-10a), 149.2 (C-11), 147.56 (C-9), 133.58 (C-14), 129.21 (C-13, C-15), 128.81 (C-12, C-16), 115.31 (C-9a, C-8a), 108.78 (C-4, C-5), 106.96 (C-1, C-2).

9-(2-Methoxyphenyl)-2,6,7-trihydroxyxanthen-3-one (4b). Yield= 71.76%**.** Anal. calcd for $C_{20}H_{14}O_6$: C 68.50, H 3.71. Found: C 68.54, H 3.78. All values are given in percentages. IR (KBr) n 3300 1715 1500 1370 1200 770 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*6) d 7.4 (m, 1H, H-14), 7.35 (d, *J* 7.9 Hz, 1H, H-16), 7.125 (m, 1H, H-15), 6.62 (d, *J* 6.81 Hz, 1H, H-13), 3.704 (s, 2H, H-1 and H-8), 3.57 (s, 2H, H-4 and H-5). ^{13}C NMR (150MHz, DMSO-*d*6) d 173.1 (C-3, C-6), 162.698 (C-2, C-7), 156.28 (C-10a, C-4a), 152.86 (C-9), 141.8 (C-11), 131.46 (C-13), 130.46 (C-14), 121.30 (C-16), 121.19 (C-15), 120.97 (C-12), 116.55 (C-8a, C-9a), 108.12 (C-4, C-5), 102.29 (C-1, C-8).

9-(4-Methoxyphenyl)-2,6,7-trihydroxyxanthen-3-one (4c). Yield= 91.00%**.** Anal. calcd for $C_{20}H_{14}O_6$: C 68.50, H 3.71. Found: C 68.43, H 3.75. All values are given in percentages. IR (KBr) n 3200 1715 1450 1390 1200 860 780 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*6) d 7.47 (d, *J* 8.4 Hz, 2H, H-12 and H-16), 7.3 (d, *J* 8.4 Hz, 2H, H-13 and H-15), 6.98 (s, 2H, H-1 and H-8), 3.97 (s, 2H, H-4 and H-5). ^{13}C NMR (150MHz, DMSO-*d*6) d 176.8 (C-3, C-6), 161.6 (C-14), 160.80 (C-2, C-7), 153.20 (C-4a, C-10a), 147.6 (C-12, C-16), 131 (C-9), 124.50 (C-11), 117.00 (C-13, C-15), 115.00 (C-9a, C-8a), 109.8 (C-4, C-5), 102.00 (C-1, C-8).

9-(2-Chlorophenyl)-2,6,7-trihydroxyxanthen-3-one (4d). Yield= 81.70% Anal. calcd for $C_{19}H_{11}ClO_5$: C 64.28, H 2.82. Found: C 64.11, H 2.76. All values are given in percentages. IR (KBr) n 3200 2700 1600 1550 1500 1056 770 735 540 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*6) d 7.78 (d, *J* 7.76 Hz, 1H, H-13), 7.682 (m, 1H, H-14), 7.74 (m, 1H, H-15), 7.54 (d, *J* 6.85 Hz, 1H, H-16), 7.18 (s, 2H, H-1 and

H-8), 6.52 (s, 2H, H-4 and H-5). ^{13}C NMR (150MHz, DMSO-*d*6) d 176.8 (C-3, C-6), 163.00 (C-2, C-7), 153.00 (C-4a, C-10a), 148.00 (C-9), 132.00 (C-11), 131.00 (C-13), 130.62 (C-14), 129.76 (C-16), 129.12 (C-15), 127.9 (C-12), 116.00 (C-8a, C-9a), 107.80 (C-4, C-5), 102.70 (C-1, C-8).

9-(4-Chlorophenyl)-2,6,7-trihydroxyxanthen-3-one (4e). Yield= 96.70%. Anal. calcd for $C_{19}H_{11}ClO_5$: C 64.28, H 2.82. Found: C 64.12, H 2.65. All values are given in percentages. IR (KBr) n 3200 1500 1400 1270 1070 780 512 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*6) d 7.76 (d, *J* 4.4 Hz, 2H, H-12 and H-16), 7.535 (d, *J* 4.4 Hz, 2H, H-13 and H-15), 7.10 (s, 2H, H-1 and H-8), 6.66 (s, 2H, H-4 and H-5). ^{13}C NMR (150MHz, DMSO-*d*6) d 172.76 (C-3, C-6), 163 (C-2, C-7), 152.8 (C-4a, C-10a), 148 (C-9), 135 (C-14, C-11), 131.80 (C-13, C-15), 131 (C-12, C-16), 116 (C-9a, C-8a), 107.80 (C-4, C-5), 102.70 (C-1, C-8).

DSC and XRPD results

In the study, 1-2 mg accurately weighed samples were run at a scanning speed of 10˚C/min. Figure 1 shows the endotherm of compound **4c**.

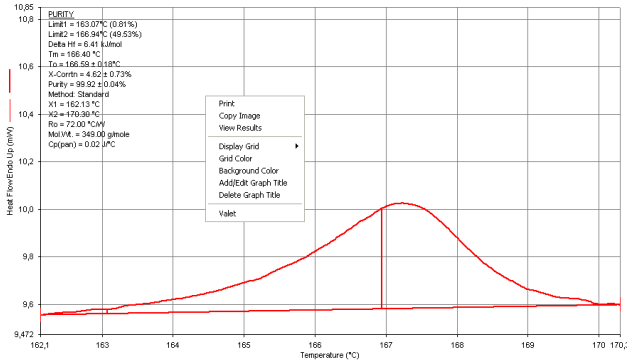


Figure 1. Endotherm of compound **4c**.

Endothermic peaks of all synthesized compounds were wide. Explanation for this is a small percentage of monocrystalline form which is thermostable. If compound has amorphic composition, endotherm will be wide because amorphic parts will soften at first and then melt when heated.

For all synthesized compounds we determined crystallinity using X-ray powder diffraction. Figure 2 shows diffractogram of compound **4e**.

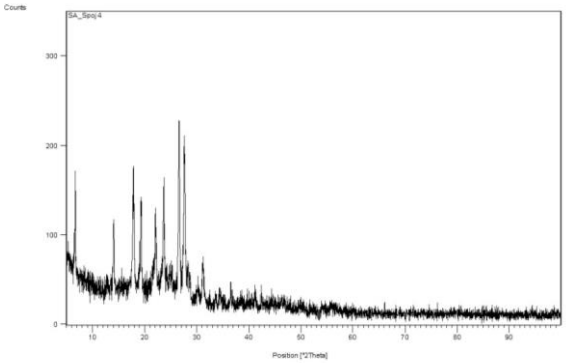


Figure 2. Diffractogram of compound **4e**.

Melting points, heat of melting, purity and crystallinity of synthesized compound are listed in Table 1.

Table 1. DSC and XRPD data for synthesized compounds.

Entry	Mw	DSC m.p. (°C)	DSC Purity (%)	DSC $\Delta H_{melt.}$ KJ/mol	XRPD Crystall. (%)
4a	319.00	357.61	100.06 ± 0.03	-2.70	25
4b	349.00	166.00	99.85 ± 0.06	9.35	30
4c	349.00	166.04	99.92 ± 0.04	6.41	10
4d	353.50	235.97	98.82 ± 0.42	29.72	20
4e	353.50	235.42	98.54 ± 0.55	36.69	38

CONCLUSION

All synthesized compounds showed wide peaks on thermograms, as a result of low percentage of monocrystalline form. This was also confirmed by X-ray diffraction of the powder (XRPD). As a result of higher percentage of amorphic composition, which is thermolabile and starts to soften at first and then to melt when heated, endotherms do not have sharp peaks.

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Summary/Sažetak

Seriji sintetiziranih ksanten-3-on derivata ispitane su termalne karakteristike diferencijalnom skenirajućom kalorimetrijom (DSC), te kristalografskom analizom praha (XRPD) utvrđen je stupanj kristaličnosti. Ksanten-3-on derivati sintetizirani su po već poznatoj proceduri, u osnovi koje su dvije Friedel-Craftsove alkilacije. Cilj ovog rada bio je utvrditi stupanj čistoće i kristaličnost sintetiziranih ksanten-3-on derivata.

Termogrami sintetiziranih spojeva pokazali su da spojevi imaju stupanj čistoće iznad 98 %, dok je kristalografska analiza praha pokazala da spojevi imaju 10-37% monokristalnih formi.