Chemistry of Heterocyclic Compounds, Vol. 46, No. 4, 2010

TRANSFORMATIONS OF 3-(1,3-DIOXOBUTAN-1-YL)-3H-CHROMEN-2-ONE DURING THE ACTION OF BROMINE

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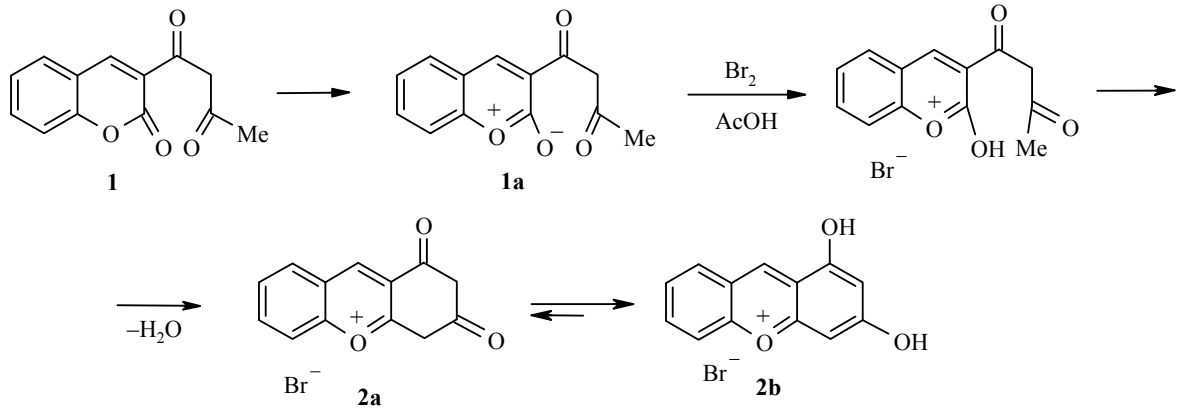
It was established that the direction of the reaction of 3-(1,3-dioxobutan-1-yl)-2H-chromen-2-one with bromine depends on the conditions under which it is carried out. In acidic media carbocyclization occurs with the formation of dihydroxanthylium bromide or hydroxyxanthene; in chloroform enolization of the carbonyl group with subsequent bromination and heterocyclization to substituted pyranochromene with the participation of the benzopyran-2-one fragment occurs.

Keywords: benzopyran-2-one, dihydroxyxanthylium bromide, hydroxyxanthene, pyranochromene, bromination.

Complex polyoxo compounds containing a benzopyran-2-one fragment exhibit antibacterial and antiphage activity [1] and are well known as inhibitors of serine protease [2]. Quite recently it was shown that 3-substituted 4-hydroxycoumarins possess anti-HIV-1 activity as nonpeptide inhibitors of HIV-proteases and integrases [3]. All this and also the structural characteristics – the presence of various types of oxo functions (ketone and lactone), the possibility of recyclization of the heterocyclic system – determine the outlook for study of their reactivity.

While continuing systematic research into the properties of oxo compounds in bromination reactions [4] we studied for the first time the behavior of 3-(1,3-dioxobutan-1-yl)-2H-chromen-2-one (**1**) with bromine under various conditions.



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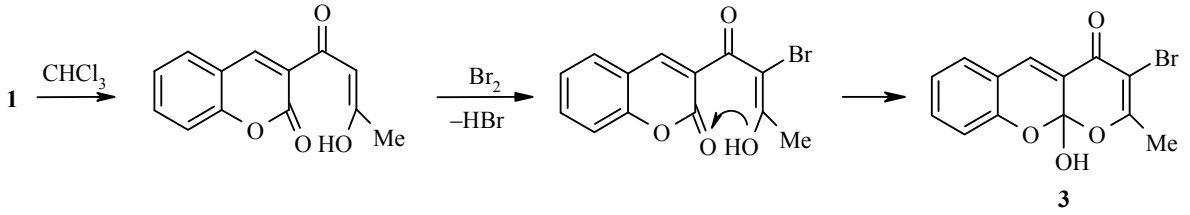
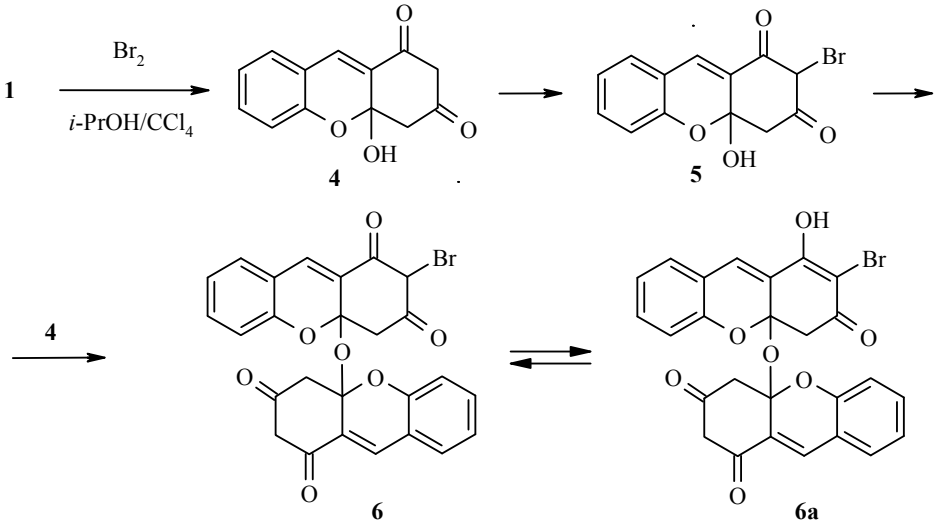
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 518-521, April, 2010. Original article submitted April 22, 2009.

It was established that the behavior of the substrate **1** depends on the nature of the employed solvent. Thus, in acetic acid 1,3-dihydroxyxanthylium bromide **2** is formed with a yield of 47%. Such behavior of the oxo compound **1** can be explained by its possible existence in the form of the bipolar ion **1a** [5], which undergoes protonation and carbocyclization.

In chloroform the enolization of the acetyl carbonyl and electrophilic addition of bromine with the participation of the enolic form of the trioxo compound **1** are facilitated, as is typical of ketones. Heterocyclization to 3-bromo-10*a*-hydroxy-2-methyl-4H,10*a*H-pyrano[2,3-*b*]chromen-4-one (**3**) then occurs.



In a mixture of 2-propanol and carbon tetrachloride bromination of one of the two molecules of the hemiketal **4** arising during carbocyclization occurs, and 4*a*-(2-bromo-1-hydroxy-3-oxo-4,4*a*-dihydro-3H-xanthen-4*a*-yloxy)-4,4*a*-dihydro-1H-xanthene-1,3(2H)-dione (**6a**) is formed as a result of dehydration of the ether. Here bromination has the usual character for systems containing 1,3-dioxocyclohexane fragments [4].



It was shown that the keto-enol equilibrium in 1,3-dihydroxyxanthylium bromide **2** is shifted fully toward the enolic form **2b**, which is confirmed by the presence of a singlet for the two protons of the hydroxyl groups at 9.00 ppm in the ^{1}H NMR spectrum. The singlet of the two protons at the double bonds of the enol fragments appears at 4.21-4.28 ppm.

Evidence for the structure of compound **3** is provided by the presence in the ^{1}H NMR spectrum of singlets for the proton of the hydroxyl group at the tertiary carbon atom at 3.86 and the protons of the methyl group at 1.23-1.25 ppm.

In the ^{1}H NMR spectrum of compound **6a** in $CDCl_3$ together with the multiplet of the eight aromatic protons in the region of 5.96-8.94 ppm there are signals for the two vinyl protons. The singlets for the H-4 protons in the bromine-substituted and unsubstituted heterocyclic systems of compound **6a** and for the H-2 in the latter appear at 3.86 and 4.01 ppm respectively. The proton of the enolic hydroxyl group (which disappears

in DMSO-d_6) is observed in the form of a broad singlet at 15.15 ppm. This fact and also the presence of a signal for the tertiary proton in the DMSO-d_6 spectrum at 4.40 ppm indicate the possible appearance of keto-enol tautomerism between the forms of the ether **6** and **6a**.

Thus, it was demonstrated for the first time that 3-(1,3-dioxobutan-1-yl)-2H-chromen-2-one (**1**) undergoes carbocyclization or heterocyclization with participation of the lactone carbonyl group, depending on the nature of the solvent.

EXPERIMENTAL

The IR spectra were recorded on an FSM 1201 IR Fourier spectrometer in hexachlorobutadiene (in the regions of 4000-1800 and 1500-1300 cm^{-1}) and in vaseline oil (in the regions of 1800-1500 and 1300-1400 cm^{-1}) in KBr cuvettes. The ^1H NMR spectra were obtained on a Varian 400 spectrometer at 25°C (400 MHz) in $CDCl_3$ (compound **1**) and a Bruker MSL-400 spectrometer (400 MHz) in $CDCl_3$ (compounds **3** and **4**) and DMSO-d_6 (compound **2b**) with TMS as internal standard. The reaction and the individuality of the products were monitored by TLC on Silufol UV-254 plates with 3:1:1 hexane–ether–acetone and 2:2:1 hexane–ethyl acetate–acetone as eluents and iodine vapor as developer.

3-(1,3-Dioxobutan-1-yl)-2H-chromen-2-one (1). This compound was obtained by the condensation of 4-hydroxycoumarin with salicylaldehyde by the known procedure [6]. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.27 (3H, s, CH_3); 6.89-7.61 (5H, m, Ar); 8.66 (1H, s, CH); 15.80 (H, s, OH).

1,3-Dihydroxanthylium Bromide (2b). To a solution of the trioxo compound **1** (2 g, 8.7 mmol) in acetic acid (20 ml) with constant stirring we added dropwise bromine (0.60 ml, 8.7 mmol). The reaction mixture was heated at 60°C for 28 h. The brown-red crystals that separated were filtered off and washed with water. The yield was 1.20 g (47%); mp 320-321 °C. IR spectrum, ν, cm^{-1}: 3300-3500 (OH); 3063 (C–H arom.); 1607 (C=C); 1560, 758 (Ar); 1530 (pyrylium cation). ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.21 (2H, s, =CH); 7.40-8.15 (5H, m, Ar); 9.00 (2H, s, OH). Found, %: C 53.40; H 3.37; Br 27.32. $C_{13}H_9BrO_3$. Calculated, %: C 53.27; H 3.09; Br 27.26.

3-Bromo-10*a*-hydroxy-2-methyl-4H,10*a*H-pyrano[2,3-*b*]chromen-4-one (3). The compound was obtained by a similar procedure using chloroform (40 ml) and bromine (1.80 ml, 26.1 mmol). The reaction time was 32 h. The yield was 1.82 g (68%) (colorless crystals); mp 180-181°C. IR spectrum, ν, cm^{-1}: 3503 (OH), 3080 (C–H arom.), 2957 (C–H aliph.), 1697 (C=C–C=O); 1548, 755 (Ar); 1244, 1043 (=C–O–C); 654 (C–Br). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, s, CH_3); 3.86 (1H, s, OH); 5.92 (1H, s, =CH); 7.16–8.03 (4H, m, Ar). Found, %: C 50.04; H 3.02; Br 25.87. $C_{13}H_9BrO_4$. Calculated, %: C 50.51; H 2.93; Br 25.85.

4*a*-(2-Bromo-1-hydroxy-3-oxo-4,4*a*-dihydro-3H-xanthen-4*a*-yloxy)-4,4*a*-dihydro-1H-xanthene-1,3(2H)-dione (6a). The compound was obtained by a similar procedure using 2-propanol (20 ml), carbon tetrachloride (5 ml), and bromine (1.20 ml, 17.4 mmol). The reaction time was 23 h, and the yield was 2.62 g (58%) (yellow crystals); mp 133-134°C. IR spectrum, ν, cm^{-1}: 3200–3600 (OH); 3055 (C–H arom); 2965 (C–H aliph.); 1727 (C(Br)–C=O); 1563, 758 (Ar); 1262, 1061 (=C–O–C); 1354, 1147 (C–OH); 650 (C–Br). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.86 (4H, s, $2CH_2$); 4.01 (2H, s, CH_2); 5.96–8.94 (10H, m, Ar); 15.15 (1H, s, OH). Found, %: C 59.73; H 3.17; Br 15.60. $C_{26}H_{17}BrO_4$. Calculated, %: C 59.90; H 3.29; Br 15.33.

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