ISSN 1070-4280, Russian Journal of Organic Chemistry, 2012, Vol. 48, No. 3, pp. 451–455. © Pleiades Publishing, Ltd., 2012. Original Russian Text © A.A. Ambartsumyan, T.T. Vasil'eva, O.V. Chakhovskaya, N.E. Mysova, V.A. Tuskaev, V.N. Khrustalev, K.A. Kochetkov, 2012, published in Zhurnal Organicheskoi Khimii, 2012, Vol. 48, No. 3, pp. 450–454.

Transformations of 4-Oxo-4*H*-chromene-3-carbaldehyde under the Action of Fe(CO)₅

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Received June 18, 2011

Abstract—Transformations of 4-oxo-4*H*-chromene-3-carbaldehyde in the presence of pentacarbonyliron and HMPA in benzene and toluene were studied, and their probable mechanism was proposed. The structure of 3-(4-oxochroman-3-ylmethyl)-4*H*-chromen-4-one was determined by spectral methods and X-ray analysis.

DOI: 10.1134/S1070428012030207

The chemistry of 3-substituted chromones has vigorously developed since 1970s when a simple and convenient procedure for the synthesis of 3-formylchromone (I) according to Vilsmeier-Haack has been proposed [1]. 3-Formylchromones are geminally activated alkenes possessing three electrophilic centers $(C^2, C^4, and 3-C)$ [2], and they are capable of acting as Michael acceptors, heterodienes, etc. In most cases, nucleophilic attack takes two possible pathways: 1,4-addition at the C^2 atom and 1,2-addition at the electrophilic carbon atom in the 3-substituent [3]. 3-Alkylchromones that cannot be obtained by direct alkylation of chromones [4] and bis-chromones linked at the 3-position [4, 5] attract strong interest from the chemical and biological viewpoints. It is known that diols derived from some natural compounds, e.g., of the menthol and α -pinene series, exhibit high physiological activity; some derivatives are tested as anticonvulsant and anticancer agents [6]. Taking into account that reduction of aldehydes and ketones provides a direct route to such monomeric and dimeric compounds, we made an attempt to use $Fe(CO)_5$ to transform formylchromone I into the corresponding diol III, as well as into difficultly accessible 3-methyl-4Hchromen-4-one (IV). The system Fe(CO)₅–HMPA was used by us previously for the reduction of haloalkanes [7] and diastereoselective synthesis of 1,2-diols [8] and other compounds [9] from aromatic aldehydes. We found that aldehyde I in the presence of $Fe(CO)_5$ - HMPA undergoes unusual transformations leading to 3-(4-oxochroman-3-ylmethyl)-4*H*-chromen-4-one (II) as the major reduction product. The reaction was carried out in benzene at 80°C (reaction time 6 h). Compound II was isolated by preparative thin-layer chromatography on silica gel using petroleum ether (bp 40–60°C)–ethyl acetate (10:1) as eluent. Compound II was obtained previously in a poor yield as by-product in the reactions of derivatives of aldehyde I, 3-aminomethylidene- or 3-hydroxymethylidenechroman-4-ones with nucleophiles [10, 11]. The structure of II was determined by ¹H NMR and IR spectroscopy, mass spectrometry, and X-ray analysis.

Figure shows the structure of molecule **II** and some its geometric parameters. Molecule **II** consists of two chromone fragments linked through a methylene



Structure of the molecule of 3-(4-oxochroman-3-ylmethyl)-4*H*-chromen-4-one (**II**) according to the X-ray diffraction data. Bond lengths: O^1-C^2 1.358(2), O^1-C^{8A} 1.369(2), $C^{11}-O^{12}$ 1.412(2), $O^{12}-C^{12A}$ 1.362(2) Å; bond angles: $C^2O^1C^{8A}$ 117.8(2), $C^3C^9C^{10}$ 113.2(2), $C^{11}O^{12}C^{12A}$ 115.3(2)°.



Scheme 1.

bridge. The bond lengths and bond angles therein are very consistent with the corresponding parameters of other chromone derivatives with known structure [12, 13]. The 4*H*-chromen-4-one fragment is planar, whereas the dihydropyran ring in the chromanone fragment adopts a *chair* conformation where the C¹¹ atom deviates by 0.582 Å from the plane formed by the other atoms of the ring. The chromone fragments are turned with respect to each other through a dihedral angle of 74.0°. Intermolecular distances in the crystal-line structure of **II** conform to the corresponding van der Waals radii.

According to [14], 4-oxo-4*H*-chromene-3-carbaldehyde can react with nucleophiles at all three electrophilic centers, so that in some cases the direction of the initial attack and subsequent transformations cannot be determined unambiguously. The structure of compound **II** indicates that the most probable site of the initial attack is the aldehyde carbonyl carbon atom. In order to elucidate the mechanism of formation of compound **II** we examined transformations of 4-oxo-4*H*chromene-3-carbaldehyde (**I**) under various conditions and obtained a number of products **II–IX** (Scheme 1).

The results are collected in table. No compound **II** was formed in the absence of $Fe(CO)_5$ or HMPA; in the presence of $Fe(CO)_5$ –HMPA, the same products, compound **II** and 3-methyl-4*H*-chromen-4-one (**IV**), were obtained at different ratios regardless of the solvent. When the reaction was carried is benzene, compound **II** was the major product, whereas compound **IV** prevailed in toluene (Scheme 1, paths *b* and *e*). In addition, small amounts of bis-chromone **V** and bis-

Run no.	Fe(CO) ₅	HMPA	Solvent	Major product	Yield, %	Conversion of I, ^a %
1	+	+	Benzene	II	10	45
2	+	+	Benzene-water, 1:1	II	9	40
3	+	_	Benzene	VII	9	20
4	—	+	Benzene	VIII	5	10
5	+	_	Toluene	III	9	40
6	+	+	Toluene	IV	22	60
7	—	+	Toluene	VII	8	20

Transformations of 4-oxo-4H-chromene-3-carbaldehyde (I) in benzene and toluene in the presence of Fe(CO)₅-HMPA

^a The conversion of **I** was determined by weighing the products isolated from the reaction mixture (¹H NMR monitoring).

chromanone **VI** were identified by mass spectrometry. In the reaction of **I** with $Fe(CO)_5$ in benzene in the absence of HMPA we detected 3,3'-(ethene-1,2-diyl)bis(4*H*-chromen-4-one) (**VII**) (Scheme 1, *c*), while in the presence of HMPA in benzene [without $Fe(CO)_5$] 4-oxo-4*H*-chromene-3-carboxylic acid (**VIII**) and 3-hydroxymethyl-4*H*-chromen-4-one (**IX**) were formed (Scheme 1, *d*), presumably as a result of disproprotionation according to Tishchenko. The properties of compounds **VIII** and **IX** were consistent with published data [15, 16]. Finally, diol **III** was detected only in the reaction mixture obtained in toluene in the presence of $Fe(CO)_5$ (without HMPA; Scheme 1, *a*).

We previously showed an important role of water traces in the Reformatsky reaction with pentafluorobenzaldehyde in toluene or benzene under the conditions corresponding to the formation of dimer according to Scheme 1 [8]. However, in the examined reactions with aldehyde I the presence of water almost did not affect the results (see table; run nos. 1, 2). In order to estimate the role of HMPA, the reaction was carried out in the presence of DMF. In this case, catalysis by traces of dimethylamine could be expected due to intermediate formation of enamine derivative of chromone I [10, 11]. Nevertheless, no reaction occurred under these conditions. Compound I also failed to react with an enamine, 3-dimethylamino-1-(2-hydroxyphenyl)prop-2-en-1-one. The reaction was carried out at 80°C in homogeneous medium (3 h), but compound II was not detected.

Our results led us to presume that compound II is formed according to Scheme 2. Reactive aldehyde I in a reducing medium (pentacarbonyliron in benzene) [7] is converted into 3-hydroxymethylidenechroman-4-one (X) [11] which undergoes aldol condensation followed by dehydration and elimination of formyl group with formation of intermediate compound XI, and double bond migration in the latter leads to more stable compound II [10].

The reaction in toluene gives only traces of **II**, for the reduction of aldehyde **I** does not stop at the stage of formation of compound **XI** but goes further to methylchromone **IV**. Compound **IV** was synthesized previously by reduction of 2-chlorochromone with zinc in acetic acid [16] or via transformation of 2-bromochromone into 2-phenylsulfanyl and 2-phenylsulfonyl derivatives [4]. In the absence of HMPA it was also possible to obtain diol **III**, which supports the scheme proposed in [9]. Diol **III** was isolated (no yield was given) as a mixture of *meso*-form and D- and L-stereo-



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isomers in the reduction of aldehyde I with zinc in acetic acid [17].

Thus we have demonstrated versatile reactivity of aldehyde I in pentacarbonyliron-containing systems which promote its transformations into various monomeric and dimeric products.

EXPERIMENTAL

The mass spectra were obtained on a Finnigan SSQ-7000 mass spectrometer. The ¹H NMR spectra were measured on a Bruker WP-300 instrument at 300 MHz using CDCl₃ as solvent; the chemical shifts are given relative to tetramethylsilane. The IR spectra were recorded on an IKS-20 spectrometer. Thin-layer chromatography was performed on Silufol UV-254 plates (Merck). The products were isolated by preparative thin-layer chromatography on glass 180×240 - and 200×200 -mm plates coated with a layer of silica gel 60 PF254 containing 30% of gypsum (Merck). All organic reagents were purified by distillation. Commercial pentacarbonyliron (98%; from Fluka) was used without additional purification.

X-Ray analysis of a single crystal of compound II was performed at the X-Ray Analysis Laboratory, Institute of Organometallic Compounds, Russian Academy of Sciences. Crystallographic data: C₁₉H₁₄O₄; M 306.30; monoclinic crystals, space group $P2_1/c$; unit cell parameters at 120(2) K: a = 9.6566(7), b =6.6457(5), c = 22.676(2) Å; $\beta = 96.632(1)^{\circ}$; V =1445.5(2) Å³; Z = 4; F(000) = 640; $d_{calc} = 1.407$ g/cm³; $\mu = 0.099 \text{ mm}^{-1}$; $R_1 = 0.060 \text{ for } 2653 \text{ independent re$ flections with $I > 2\sigma(I)$; $wR_2 = 0.163$ for all 3465 independent reflections; goodness of fit 1.008. Total of 14040 reflection intensities ($R_{int} = 0.032$) were measured on a Bruker SMART 1K CCD diffractometer $[\lambda(MoK_{\alpha})]$ irradiation, graphite monochromator, φ - and ω -scanning, $\theta_{max} = 28^\circ$]. The structure was solved by direct methods and was refined in anisotropic approximation for non-hydrogen atoms. The positions of hydrogen atoms were calculated on the basis of geometry considerations and were refined in isotropic approximation $[U_{iso}(H) = 1.2U_{eq}(C)]$. All calculations were performed using SHELXTL software package [18]. The complete set of crystallographic data for compound II was deposited to the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk/ data request/cif; entry no. CCDC 794281).

3-(4-Oxochroman-3-ylmethyl)-4*H***-chromen-4one (II). 4-Oxo-4***H***-chromene-3-carbaldehyde (I), 0.174 g (1 mmol), was dissolved in 1 ml of benzene,**

0.7 ml (4 mmol) of HMPA and 0.27 ml (2 mmol) of Fe(CO)₅ were added, and the mixture was heated for 6 h at 80°C, the progress of the reaction being monitored following evolution of carbon(II) oxide and by TLC (petroleum ether-ethyl acetate 10:1). When the reaction was complete, the mixture was treated with 30 ml of 1 N hydrochloric acid and washed with water, the organic phase was dried over MgSO₄, and the product was isolated by preparative TLC on 180×240mm glass plates [silica gel 60 PF₂₅₄ containing 30% of gypsum; petroleum ether (bp 40-60°C)-ethyl acetate, 10:1]. Yield 0.0306 g (10%), mp 120°C. IR spectrum (mineral oil), v, cm⁻¹: 3061 (C-H_{arom}); 2923, 2853 (C-H); 1685, 1633 (C=O); 1607, 1574, 1465 (C=C, C=C_{arom}). ¹H NMR spectrum, δ , ppm: 2.69–2.76 and 2.99–3.05 (2H, CCH₂CH, AB part of ABX spin system, $J_{AX} = 6.3, J_{BX} = 6.3, J_{AB} = 14.0$ Hz), 3.16–3.26 (1H, X part of ABX spin system, $J_{AX} = 5.0$, $J_{BX} = 5.0$, $J_{AB} =$ 11.5 Hz), 6.93-7.03 m (2H, Harom), 7.38-7.49 m (3H, H_{arom}), 7.63–7.69 m (1H, H_{arom}), 7.86–7.89 q (1H, Harom), 7.97 s (1H, OCH), 8.20-8.23 q (1H, Harom). Mass spectrum, m/z (I_{rel} , %): 306 (6) [M]⁺, 185 (15) $[M - C_7 H_4 O_2]^+$, 160 (60) $[185 - C_2 H_2]^+$, 147 (100) $[160 - CH_2]^+$, 121 (12) $[147 - C_2H_2]^+$, 92 (10) $[121 - C_2H_2]^+$ $CO]^+, 65 (7) [92 - CO]^+.$

3,3'-(1,2-Dihydroxyethane-1,2-diyl)bis(4*H***-chromen-4-one) (III) was synthesized as described above for compound II in toluene in the absence of HMPA. Yield 0.0315 g (9%), mp 128–130°C. IR spectrum (mineral oil), v, cm⁻¹: 3361 (O–H); 3085 (C–H_{arom}); 2923 (C–H, O–H); 1650 (C=O); 1608, 1573, 1466 (C=C_{arom}). ¹H NMR spectrum, \delta, ppm: 4.65 s (2H, OH), 4.67 s (2H, CHOH), 7.45–7.55 m (4H, H_{arom}), 7.71–7.79 m (2H, H_{arom}), 8.01 s (1H, OCH), 8.17 s (1H, OCH), 8.28–8.31 m (2H, H_{arom}). Mass spectrum:** *m/z* **175 (***I***_{rel} 100 %) [***M***/2]⁺.**

3-Methyl-4*H***-chromen-4-one (IV)** was isolated as described above for compound **II**, but the reaction was carried out in toluene. Yield 0.077 g (22%), mp 62–64°C. ¹H NMR spectrum, δ , ppm: 2.04–2.05 d (1H, CH₃), 7.36–7.44 m (2H, H_{arom}), 7.62–7.67 m (1H, H_{arom}), 7.80–7.81 d (1H, OCH), 8.23–8.26 q (1H, H_{arom}). Mass spectrum, *m*/*z* (*I*_{rel}, %): 160 (100) [*M*]⁺, 145 (3) [*M* – CH₃]⁺, 120 (40) [145 – C₂H₂]⁺, 92 (50) [12 – CO]⁺, 63 (20) [92 – CO]⁺.

Compounds V–VII were identified in reaction mixtures by mass spectrometry.

4-Oxo-4H-chromene-3-carboxylic acid (VIII) and 3-hydroxymethyl-4H-chromen-4-one (IX) were isolated in the reaction carried out as described above for compound II in the absence of Fe(CO)₅. Compound VIII. Yield 0.01 g (5%), mp 138– 140°C. IR spectrum (mineral oil), v, cm⁻¹: 3405 (O–H); 3077 (C–H_{arom}); 1665 (C⁴=O); 1637 (C=O, acid); 1614, 1585, 1561 (C=C, C=C_{arom}). ¹H NMR spectrum, δ , ppm: 6.95–7.00 m (1H, H_{arom}), 7.16– 7.19 d (1H, H_{arom}), 7.59–7.66 m (2H, H_{arom}), 7.87 m (2H, H_{arom}), 7.87 s (1H, OCH), 12.01 s (1H, COOH).

Compound IX. Yield 0.0088 g (5%), mp 65–67°C. ¹H NMR spectrum (300 MHz, CDCl₃) δ , ppm: 4.34– 4.36 t (2H, CH₂), 5.49 s (1H, OH), 7.53–7.57 m (2H, H_{arom}), 7.78–7.80 t (1H, H_{arom}), 8.22 s (1H, H_{arom}), 8.34– 8.37 d (1H, H_{arom}).

This study was performed under financial support by the Chemistry and Materials Science Department of the Russian Academy of Sciences (program no. 9, "Biomolecular and Medicinal Chemistry") and by the Russian Foundation for Basic Research (project no. 09-03-01097).

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