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Reactions of Zinc Enolates Derived from 1-Aryl-2-bromo-2-phenylethanone and 2-Bromoindan-1-one with Alkyl 2-Oxochromene- and 6-Bromo-2-oxochromene-3-carboxylates

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Abstract — Zinc enolates derived from 1-aryl-2-bromo-2-phenylethanone react with alkyl 2-oxochromene-3-carboxylates and methyl 6-bromo-2-oxochromene-3-carboxylate to give, respectively, alkyl 4-(2-aryl-2-oxo-1-phenylethyl)-2-oxochroman-3-carboxylates and methyl 6-bromo-4-(2-aryl-2-oxo-1-phenylethyl)-2-oxochroman-3-carboxylate as a single stereoisomer. Zinc enolates derived from 2-bromoindan-1-one react with alkyl 2-oxochromene-3-carboxylates to give alkyl 2-oxo-4-(1-oxoindan-2-yl)chroman-3-carboxylates as a single stereoisomer.

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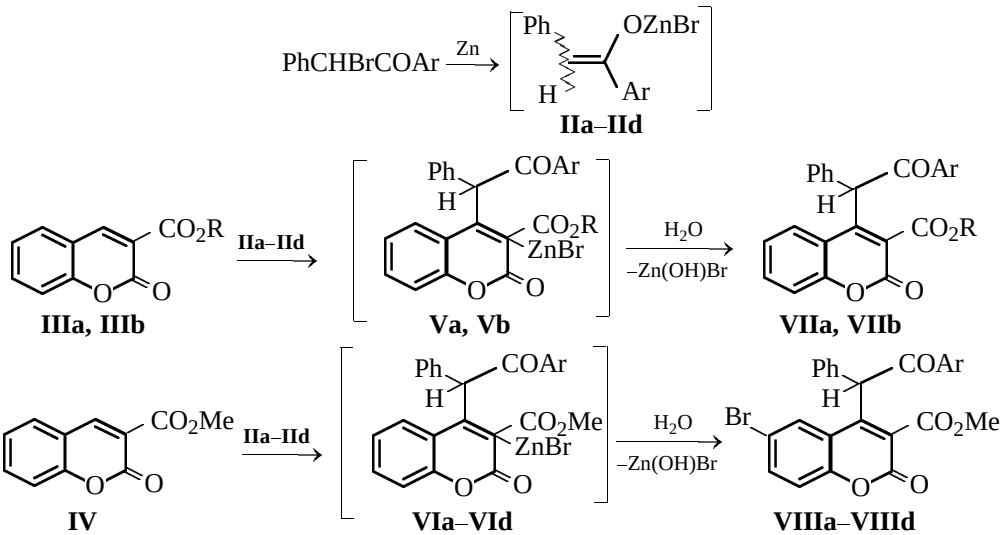
It is known that carbon-centered nucleophiles are capable of adding at the ester or lactone carbonyl carbon atom or C^4 in alkyl 2-oxochromene-3-carboxylates [1–3]. While studying reactions of zinc enolates **IIa**–**IId** derived from 1-aryl-2-bromo-2-phenylethanone with alkyl 2-oxochromene-3-carboxylates **IIIa** and **IIIb** and methyl 6-bromo-2-oxochromene-3-carboxylate (**IV**), we found that the attack by the nucleophile is directed exclusively at the C^4 atom of the electrophilic substrate; after hydrolysis of primary addition products **Va**, **Vb**, and **VIa**–**VId**, we isolated alkyl 4-(2-aryl-2-oxo-1-phenylethyl)-2-oxochroman-3-carboxylates **VIIa** and **VIIb** and methyl 4-(2-aryl-2-oxo-1-phenylethyl)-6-bromo-2-oxochroman-3-carboxylates **VIIIa**–**VIIId**, respectively (Scheme 1).

Scheme 1.

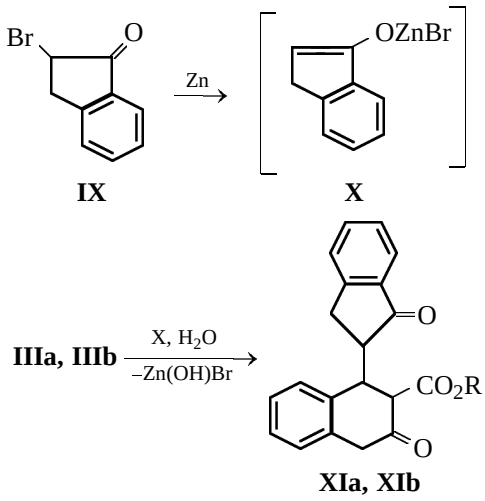


I, II, VI, VIII, Ar = 4-MeC_6H_4 (**a**), 4-EtC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-BrC_6H_4 (**d**); **III**, R = Me (**a**), Et (**b**); **V, VII**, R = Me, Ar = 4-MeC_6H_4 (**a**); R = Et, Ar = 4-ClC_6H_4 (**b**).

The reaction starts after mixing all components (the mixture spontaneously boils up) and is accompanied by dissolution of crystalline initial substances **IIIa**, **IIIb**, and **IV**. The structure of products **VIIa**, **VIIb**, and **VIIIa**–**VIIId** was proved by their analytical data and ^{1}H NMR and IR spectra. The IR spectra of **VIIa**, **VIIb**, and **VIIIa**–**VIIId** characteristically contained absorption bands in the regions 1665–1685, 1735–1745, and 1770–1790 cm^{-1}, which belong to stretching vibrations of the ketone, ester, and lactone carbonyl groups, respectively. The ^{1}H NMR spectra of alkyl 4-(2-aryl-2-oxo-1-phenylethyl)-2-oxochroman-3-carboxylates **VIIa** and **VIIb** and methyl 4-(2-aryl-2-oxo-1-phenylethyl)-6-bromo-2-oxochroman-3-carboxylates **VIIIa**–**VIIId** (see Experimental) indicated that these compounds were formed as a single stereoisomer.

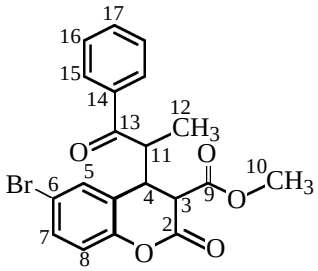
We then examined reactions of electrophilic substrates **IIIa** and **IIIb** with zinc enolate **X** derived from 2-bromoindan-1-one (**IX**). These reactions followed the above scheme to produce alkyl 2-oxo-4-(1-oxoindan-2-yl)chromane-3-carboxylates **XIa** and **XIb** as a single stereoisomer (Scheme 2).

Scheme 2.



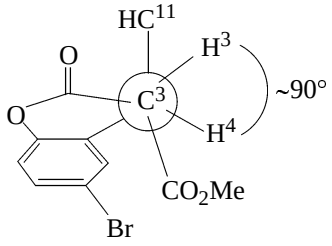
XI, R = Me (**a**), Et (**b**).

The elemental analyses and ^{1}H NMR and IR spectra of **XIa** and **XIb** are given in Experimental. Compounds **VIIa**, **VIIb**, **VIIIa**–**VIIId**, **XIa**, and **XIb**, like their analogs synthesized by us previously [4], are characterized by a coupling constant between protons in positions 3 and 4 ($J_{3,4}$) of <2 Hz. In order to get further information on the product structure we analyzed the ^{1}H and ^{13}C NMR spectra of methyl 6-bromo-4-(1-methyl-2-oxo-2-phenylethyl)-2-oxochroman-3-carboxylate (**XII**) [4] as model compound. Signals from carbon atoms attached to protons were assigned using 2D HSQC heteronuclear technique (see Experimental).



XII

Ester **XII** showed in the ^{1}H NMR spectrum (400 MHz, DMSO-d_6) signals typical of CH protons at δ, ppm (J, Hz): 3.86 d. d (1H, 4-H, J_4, 11 = 7.3, $J_{4,3}$ = 1.6), 3.89 d.q (1H, 11-H, J_{11}, 4 = 7.3, $J_{11,12}$ = 6.7), 4.40 d (1H, 3-H, $J_{3,4}$ = 1.6). Here, the coupling constant $J_{3,4}$ equal to 1.6 Hz is characteristic. Bojilova [5] reported a $J_{3,4}$ value of 1.5 Hz for methyl 2-oxo-4-trichloromethylchromene-3-carboxylate. This value was assigned to trans arrangement of the substituents at C^3 and C^4 and equatorial and pseudoequatorial orientations of the 3-H and 4-H atoms in the pyran ring. Taking these data into account, both ester **XII** and the other compounds of this series were assigned *trans* configuration where the 3-H and 4-H protons in the pyran ring occupy equatorial (or pseudoequatorial) positions with a dihedral angle HC^{3}C^{4}H of about 90°.



EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra of compounds **VIIa, VIIb, VIIIa, VIIIb, VIIId, XIa**, and **XIb** in $CDCl_3$ and of **VIIIc** in DMSO-d_6 were recorded on a Tesla BS-567A spec trometer (100 MHz) using HMDS as internal reference; the spectrum of **VIIIc** in $CDCl_3$ was also measured on a Mercury Plus-300 instrument (300 MHz); and compounds **VIIb** and **VIIId** were examined as solutions in DMSO-d_6 on a Bruker DRX-500 spectrometer (500 MHz) using TMS as internal reference. The ^{1}H and ^{13}C NMR spectra of ester **XII** in DMSO-d_6 were recorded on a Bruker

DRX-400 instrument at 400 and 100 MHz, respectively, using TMS as internal reference.

Methyl 2-oxo-4-(2-oxo-1-phenyl-2-p-tolylethyl)-chroman-3-carboxylate (VIIa). Methyl 2-oxochromene-3-carboxylate (**IIIa**), 0.01 mol, and 2-bromo-2-phenyl-1-*p*-tolylethanone (**Ia**), 0.012 mol, were added to a mixture of 3 g of zinc (prepared as fine turnings), 8 ml of diethyl ether, and 8 ml of ethyl acetate. The mixture was heated until a reaction started, and the reaction then occurred spontaneously. When the reaction was complete, the mixture was heated for an additional 15 min under reflux, treated with 10% hydrochloric acid, and extracted with diethyl ether. The extract was washed with a 10% solution of sodium hydrogen carbonate until neutral reaction and dried over sodium sulfate, the solvent was distilled off, and the residue was purified by double recrystallization from methanol. Yield 60%, mp 137–140°C. IR spectrum, ν, cm^{-1}: 1685 (C=O, ketone), 1740 (C=O, ester), 1790 (C=O, lactone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.21 s (3H, $CH_3C_6H_4$), 3.38 s (1H, 3-H), 3.42 s (3H, OCH_3), 4.41 m (2H, 4-H, 4-CH), 6.75–7.70 m (12H, $CH_3C_6H_4$, C_6H_5, C_6H_4). Found, %: C 75.35; H 5.35. $C_{26}H_{22}O_5$. Calculated, %: C 75.32; H 5.33.

Ethyl 4-[2-(4-chlorophenyl)-2-oxo-1-phenylethyl]-2-oxochroman-3-carboxylate (VIIb) was synthesized in a similar way using ethyl 2-oxochromene-3-carboxylate (**IIIb**) and 1-(4-chlorophenyl)-2-bromo-2-phenylethanone (**Ic**) as initial compounds. Yield 89%, mp 165–166°C. IR spectrum, ν, cm^{-1}: 1685 (C=O, ketone), 1735 (C=O, ester), 1785 (C=O, lactone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): in $CDCl_3$: 0.88 t (3H, CH_2CH_3, *J* = 7), 3.32 s (1H, 3-H), 3.85 q (2H, CH_2CH_3, *J* = 7), 4.39 m (2H, 4-H, 4-CH), 6.75–7.61 m (12H, ClC_6H_4, C_6H_5, C_6H_4); in DMSO-d_6: 0.89 t (3H, CH_2CH_3, *J* = 7), 3.41 s (1H, 3-H), 3.94 q (2H, CH_2CH_3, *J* = 7), 4.35 d (1H, 4-H, *J* = 10), 4.97 d (1H, 4-CH, *J* = 10), 7.96 d and 7.08–7.45 m (12H, ClC_6H_4, C_6H_5, C_6H_4). Found, %: C 69.05; H 4.40. $C_{27}H_{19}ClO_5$. Calculated, %: C 69.07; H 4.43.

Methyl 4-(2-aryl-2-oxo-1-phenylethyl)-6-bromo-2-oxochroman-3-carboxylates VIIIa–VIIId were synthesized as described above for compound **VIIa** using methyl 5-bromo-2-oxochromene-3-carboxylate (**IIIb**) as initial compound.

Methyl 6-bromo-2-oxo-4-(2-oxo-1-phenyl-2-*p*-tolylethyl)chroman-3-carboxylate (VIIIa). Yield 70%, mp 171–173°C. IR spectrum, ν, cm^{-1}: 1665 (C=O, ketone), 1740 (C=O, ester), 1770 (C=O, lactone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.20 s (3H, $C_6H_4CH_3$), 3.38 s (1H, 3-H), 3.46 s (3H, OCH_3), 4.39 m (2H, 4-H, 4-CH), 6.72–7.64 m (12H, $4\text{-}CH_3C_6H_4$, C_6H_5, BrC_6H_3). Found, %: C 63.30; H 4.29; Br 16.20. $C_{26}H_{21}BrO_5$. Calculated, %: C 63.32; H 4.28; Br 16.23.

Methyl 6-bromo-4-[2-(4-ethylphenyl)-2-oxo-1-phenylethyl]-2-oxochroman-3-carboxylate (VIIIb). Yield 83%, mp 197–199°C. IR spectrum, ν, cm^{-1}: 1670 (C=O, ketone), 1745 (C=O, ester), 1780 (C=O, lactone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.11 t (3H, CH_2CH_3, *J* = 7), 2.49 q (2H, CH_2CH_3, *J* = 7), 3.37 s (1H, 3-H), 3.45 s (3H, OCH_3), 4.38 m (2H, 4-H, 4-CH), 6.70–7.71 m (12H, $4\text{-}EtC_6H_4$, C_6H_5, BrC_6H_3). Found, %: C 63.92; H 4.57; Br 15.75. $C_{26}H_{21}BrO_5$. Calculated, %: C 63.91; H 4.54; Br 15.77.

Methyl 6-brom-4-[2-(4-chlorophenyl)-2-oxo-1-phenylethyl]-2-oxochroman-3-carboxylate (VIIIc). Yield 60%, mp 208–209°C. IR spectrum, ν, cm^{-1}: 1670 (C=O, ketone), 1740 (C=O, ester), 1780 (C=O, lactone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): in $CDCl_3$: 3.41 s (1H, 3-H); 3.51 s (3H, OCH_3); 4.35 d and 4.44 d (2H, 4-H, 4-CH, *J* = 10 Hz); 6.83 d, 7.18–7.38 m, 7.52 d, and 7.65 d (12H, $4\text{-}ClC_6H_4$, C_6H_5, BrC_6H_3); in DMSO-d_6: 3.42 s (1H, 3-H), 3.46 s (3H, OCH_3), 4.25 d (1H, 4-H, *J* = 10) 4.74 d (1H, 4-CH, *J* = 10), 7.05–7.40 m and 7.75 d (12H, $4\text{-}ClC_6H_4$, C_6H_5, BrC_6H_3). Found, %: C 58.45; H 3.53; Br 15.55. $C_{26}H_{21}BrO_5$. Calculated, %: C 58.41; H 3.55; Br 15.52.

Methyl 6-bromo-4-[2-(4-bromophenyl)-2-oxo-1-phenylethyl]-2-oxochroman-3-carboxylate (VIIId). Yield 56%, mp 189–191°C. IR spectrum, δ, cm^{-1}: 1685 (C=O, ketone), 1735 (C=O, ester), 1785 (C=O, lactone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): in $CDCl_3$: 3.36 s (1H, 3-H), 3.48 s (3H, OCH_3), 4.32 m (2H, 4-H, 4-CH), 6.70–7.55 m (12H, $4\text{-}BrC_6H_4$, C_6H_5, BrC_6H_3); in DMSO-d_6: 3.52 s (3H, OCH_3), 3.57 s (1H, 3-H), 4.33 d (1H, 4-H, *J* = 8.5), 5.03 d (1H, 4-CH, *J* = 8.5), 7.03–7.56 m and 7.94 d (12H, $4\text{-}BrC_6H_4$, C_6H_5, BrC_6H_3). Found, %: C 53.79; H 3.25; Br 28.63. $C_{26}H_{21}BrO_5$. Calculated, %: C 53.82; H 3.27; Br 28.65.

Methyl 2-oxo-4-(1-oxoindan-2-yl)chroman-3-carboxylate (XIa) was synthesized as described above for compound VIIa using methyl 2-oxochromene-3-carboxylate (**IIIa**) and 2-bromoindan-1-one (**IX**) as initial compounds. Yield 70%, mp 169–170°C. IR spectrum, ν, cm^{-1}: 1715 (C=O, ketone), 1755 (C=O, ester), 1795 (C=O, lactone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.50–3.20 m (3H, CH_2CH, 4-CH), 3.57 s (3H, OCH_3), 4.10 d (1H, 4-H, *J* = 5.5), 4.23 s (1H, 3-H), 6.70–7.70 m (8H, $2C_6H_4$). Found, %: C 71.42; H 4.79. $C_{20}H_{16}O_5$. Calculated, %: C 71.40; H 4.82.

Ethyl 2-oxo-4-(1-oxoindan-2-yl)chroman-3-carboxylate (XIb) was synthesized as described above for compound **VIIa** using ethyl 2-oxochromene-3-carboxylate (**IIIb**) and 2-bromoindan-1-one (**IX**) as initial compounds. Yield 80%, mp 143–144°C. IR spectrum, ν, cm^{-1}: 1720 (C=O, ketone), 1755 (C=O, ester), 1790 (C=O, lactone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.11 t (3H, OCH_2CH_3, *J* = 7), 2.50–3.20 m (3H, CH_2CH, 4-CH), 4.00 q (2H, OCH_2CH_3, *J* = 7), 4.10–4.20 m (2H, 3-H, 4-H), 6.60–7.70 m (8H, $2C_6H_4$). Found, %: C 71.99; H 5.18. $C_{21}H_{18}O_5$. Calculated, %: C 79.96; H 5.20.

Methyl 6-bromo-4-(1-methyl-2-oxo-2-phenylethyl)-2-oxochroman-3-carboxylate (XII). Yield 68%, mp 116–118°C. IR spectrum, ν, cm^{-1}: 1675 (C=O, ketone), 1720–1735 (C=O, ester), 1780 (C=O, lactone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14 d (3H, 12-H, *J* = 6.7), 3.58 s (3H, 10-H), 3.86 d. d (1H, 4-H, $J_{4,11}$ = 7.3, $J_{4,3}$ = 1.6), 3.89 d.q (1H, 11-H, $J_{11,4}$ = 7.3, $J_{11,12}$ = 6.7), 4.40 d (1H, 3-H, $J_{3,4}$ = 1.6), 7.10 d (1H, 8-H, *J* = 8.7), 7.46 d.d (1H, 7-H, *J* = 8.7, 2.4), 7.49 d (1H, 5-H, *J* = 2.4), 7.50 m (2H, 16-H), 7.62 t.t (1H, 17-H, *J* = 7.4, 1.3), 7.91 d.d (2H, 15-H, *J* = 8.5, 1.3). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ_C, ppm: 14.08 (C^{12}), 40.23 (C^4), 43.27 (C^{11}), 47.82 (C^3), 53.26 (C^{10}), 116.47 (C^{4a}), 118.84 (C^8), 124.80 (C^6), 128.26 (C^{15}), 128.81 (C^{16}), 131.99 and 132.06 (C^5, C^7), 133.58 (C^{17}), 135.50 (C^{14}), 149.95 (C^{8a}), 163.14 (C^9), 167.21 (C^2), 201.68 (C^{13}). Found, %: C 57.42; H 4.02; Br 19.13. $C_{26}H_{21}BrO_5$. Calculated, %: C 57.57; H 4.11; Br 19.15.

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