Russian Journal of Organic Chemistry, Vol. 40, No. 10, 2004, pp. 1487–1489. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 10, 2004, pp. 1536–1538.

Reactions of Zinc Enolates Derived from 1-Aryl-2-bromoalkanones with 3-Acyl-6-bromochromen-2-ones

V. V. Shchepin, A. E. Korzun, S. N. Shurov, and M. I. Vakhrin

Perm State University, ul. Bukireva 15, Perm, 614990 Russia

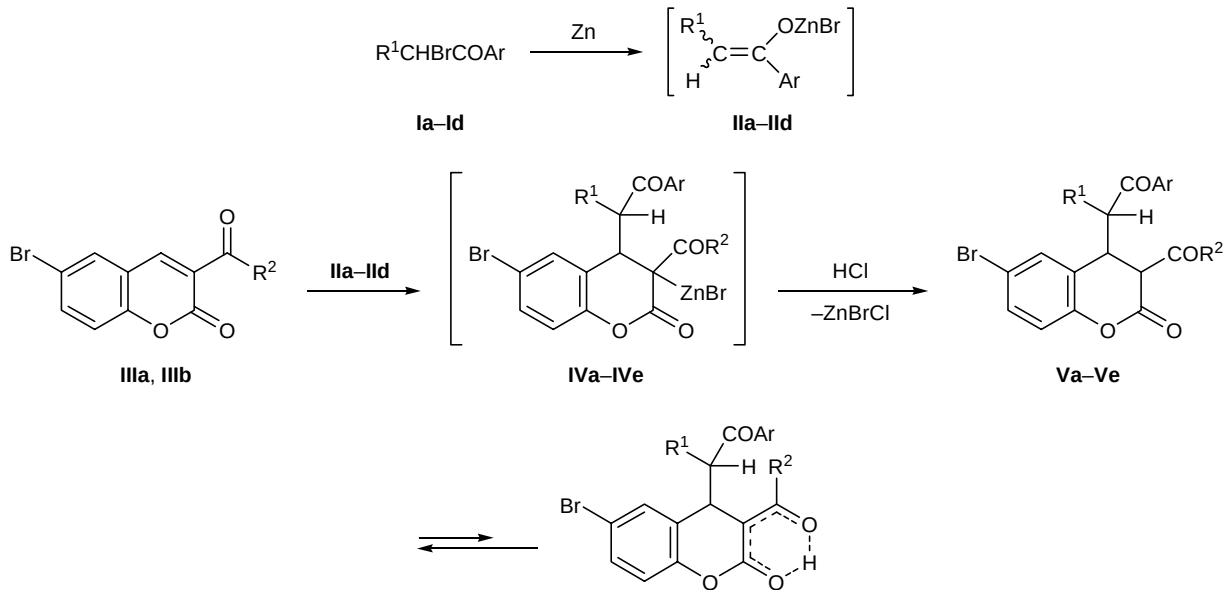
Received November 15, 2002

Abstract—Zinc enolates derived from 1-aryl-2-bromoalkanones react with 3-acyl-6-bromochromen-2-ones to give 3-acetyl(benzoyl)-6-bromo-4-(2-aryl-2-oxo-1-R-ethyl)chromen-2-ones as a single diastereoisomer.

In keeping with published data, 3-acylchromen-2-ones (3-acylcoumarins) are capable of taking up diethyl malonate, ethyl acetoacetate, and ethyl cyanoacetate at the double bond in the presence of bases [1]. We have found no published data on reactions of 3-acylchromen-2-ones with metal enolates derived from ketones. Our experiments showed that zinc enolates **II** obtained from 1-aryl-2-bromoalkanones **I** react with 3-acetyl- and 3-benzoyl-6-bromochromen-2-ones via regioselective attack on the C^4 atom to give intermediate **III**; the subsequent hydrolysis affords 3-acetyl- and 3-benzoyl-6-bromo-4-(2-aryl-2-oxo-1-R-ethyl)chroman-2-ones **Va**–**Ve**. The reaction occurs in diethyl ether–ethyl acetate at the boiling point of the mixture.

The structure of compounds **Va**–**Ve** was proved by the data of elemental analysis and IR and NMR spectroscopy. The IR spectra of **Va**–**Ve** contained characteristic absorption bands at 1670, 1710, and 1770 cm^{-1} due to stretching vibrations of the ketone and lactone carbonyl groups. The ^1H NMR spectral data indicate that compounds **Va**–**Ve** are formed as a single diastereoisomer which exists in the ketone form (K). However, in DMSO-d_6 we detected considerable amounts of two enol forms which may be denoted as E1 and E2. The ^1H NMR spectrum of 3-acetyl-6-

Scheme 1.

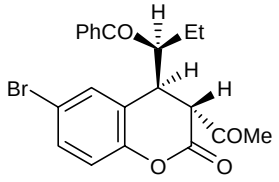


I, **II**, R^1 = Me, Ar = Ph (**a**), 4-ClC_6H_4 (**b**), 4-BrC_6H_4 (**c**); R^1 = Et, Ar = Ph (**d**); **III**, R^2 = Me (**a**), Ph (**b**); **IV**, **V**, $R^1 = R^2$ = Me, Ar = Ph (**a**), 4-ClC_6H_4 (**b**), 4-BrC_6H_4 (**c**); R^1 = Et, R^2 = Me, Ar = Ph (**d**); R^1 = Me, R^2 = Ph, Ar = 4-BrC_6H_4 (**e**).

1070-4280/04/4010-1487

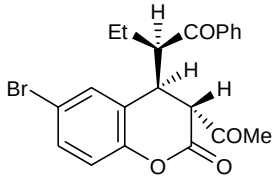
bromo-4-(2-oxo-2-phenyl-1-methylethyl)chroman-2-one (**Va**), apart from signals belonging to the aromatic protons, contained the following signals (DMSO-d_6–CCl_4, 1:3), δ, ppm: K, 46%: 1.15 d (3H, CH**Me**), 2.25 s (3H, COMe), 3.70–3.80 m (1H, C**H**Me), 3.90 d (1H, C**H**CHCOMe), 3.94 s (1H, C**H**COMe); E1, 25%: 1.02 d (3H, CH**Me**), 2.12 s (3H, MeC=C), 3.70–3.80 m (1H, C**H**Me), 4.11 d (1H, CHC=C), 12.46 s (1H, OH); E2, 29%: 0.95 d (3H, CH**Me**), 2.30 s (3H, MeC=C), 3.70–3.80 m (1H, C**H**Me), 4.48 d (1H, CHC=C, J = 3 Hz), 11.14 s (1H, OH). We failed to unambiguously determine the structure of the enol tautomers.

It should be noted that the 3-H signal in the ^{1}H NMR spectra of compounds **Va**–**Vc** and **Ve**, recorded at 60 MHz (RYa-2310), is a singlet, while the corresponding signal in the spectrum of **Vd**, recorded at 500 MHz (Bruker DRX) appears as a doublet with a coupling constant $J_{3,4}$ of 1.5 Hz. In order to rationalize these results, we performed quantum-chemical calculations (SCF MO LCAO, MNDO–PM3 [2]) of the bond lengths, bond and dihedral angles, and enthalpies of formation (ΔH_f) of isomeric structures of 3-acetyl-6-bromo-4-(1-benzoylpropyl)chroman-2-one (**Vd**). Compounds **V** possess three chiral centers: C^3 and C^4 atoms in the pyran ring and the exocyclic carbon atom (C^α); therefore, eight stereoisomeric structures are possible. Each stereoisomer should be characterized by its own value of the dihedral angle HC^3C^4H (φ) and hence by a specific vicinal coupling constant $J_{3,4}$ in the ^{1}H NMR spectrum.



A

(3*R*,4*S*,α*S*)
ΔH_f = –439.8 kJ/mol



B

(3*R*,4*S*,α*R*)
ΔH_f = –441.1 kJ/mol

According to the calculations, the most stable are stereoisomers **A** and **B** having (3*R*,4*S*) configuration. This follows from analysis of the ΔH_f values. The configuration of C^α only slightly affects the enthalpy of formation. The calculated dihedral angles φ in isomers **A** and **B** are 81.3 and 78.8°, respectively. The corresponding coupling constants $J_{3,4}$, calculated according to the Karplus equation using the Bothner-By parameters [3], are 2.1 and 2.2 Hz. The other stereoisomers of **Vd** are characterized by different dihedral angles φ, and the corresponding coupling constants $J_{3,4}$ range from 4.4 to 11.8 Hz. In the experimental high-resolution ^{1}H NMR spectra, the 3-H signal is a doublet with a coupling constant $J_{3,4}$ of 1.5 Hz, which suggests a weak interaction with the 4-H proton. Such interaction is possible only in stereoisomers **A** and **B**.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra of compounds **Va**–**Vc** and **Ve** were obtained from solutions in $CDCl_3$ on an RYa-2310 spectrometer (60 MHz) using HMDS as internal reference. The ^{1}H NMR spectra of **Va**–**Vc** and **Ve** in DMSO-d_6–CCl_4 (1:3) and of **Vd** in DMSO-d_6 were also measured on a Bruker DRX instrument operating at 500 MHz with TMS as internal reference. Quantum-chemical calculations were performed on a Pentium-200 MMX computer using MOPAC 7.0 software package [4].

3-Acyl-6-bromo-(2-aryl-2-oxo-1-R-ethyl)chroman-2-ones Va–Ve. To a mixture of 3 g of zinc prepared as fine turnings, 7 ml of diethyl ether, and 7 ml of ethyl acetate we added 0.007 mol of 3-acetyl- or 3-benzoyl-6-bromochromen-2-one **IIIa** or **IIIb** and 0.001 mol of 1-aryl-2-bromoalkanone **Ia**–**Id**. The mixture was heated to initiate the reaction which then occurred spontaneously. When the reaction was complete, the mixture was heated for 15 min under reflux, cooled, treated with 10% hydrochloric acid, and extracted with diethyl ether. The organic phase was separated, washed with a solution of sodium hydrogen carbonate until neutral reaction, and dried over sodium sulfate. The solvent was distilled off, and the products were purified by double recrystallization from methanol.

3-Acetyl-6-bromo-4-(1-methyl-2-oxo-2-phenylethyl)chroman-2-one (Va). Yield 40%, mp 115–118°C. ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 1.10 d (3H, CH**Me**), 2.17 s (3H, COMe), 3.40–4.00 m (1H, C**H**Me), 3.78 s (2H, CHCH), 6.80–8.00 m (8H, H_{arom}); in DMSO-d_6–CCl_4 (1:3): 1.15 d (3H, CH**Me**), 2.25 s (3H, COMe), 3.70–3.80 m (1H, C**H**Me), 3.90 d (1H, C**H**CHCOMe), 3.94 s (1H, C**H**COMe) (K, 46%); 1.02 d (3H, CH**Me**), 2.12 s (3H, MeC=C), 3.70–3.80 m (1H, C**H**Me), 4.11 d (1H, CHC=C), 12.46 s (1H, OH) (E1, 25%); 0.95 d (3H, CH**Me**), 2.30 s (3H, MeC=C), 3.70–3.80 m (1H, C**H**Me), 4.48 d (1H, CHC=C, J = 3 Hz), 11.14 s (1H, OH) (E2, 29%); 6.85–

8.05 m (8H, H_{arom}). Found, %: C 59.69; H 4.15; Br 19.75. $C_{20}H_{17}BrO_4$. Calculated, %: C 59.87; H 4.27; Br 19.91.

3-Acetyl-6-bromo-4-[2-(4-chlorophenyl)-1-methyl-2-oxoethyl]chroman-2-one (Vb). Yield 65%, mp 145–147°C. ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 1.10 d (3H, CH**Me**), 2.18 s (3H, COMe), 3.40–4.00 m (1H, C**H**Me), 3.78 s (2H, CHCH), 6.80–8.00 m (7H, H_{arom}); in DMSO-d_6–CCl_4 (1:3): 1.13 d (3H, CH**Me**), 2.25 s (3H, COMe), 3.70–3.80 m (1H, C**H**Me), 3.89 d (1H, C**H**CHCOMe), 3.95 s (1H, C**H**COMe) (K, 42%); 1.02 d (3H, CH**Me**), 2.12 s (3H, MeC=C), 3.72–3.82 m (1H, C**H**Me), 4.11 d (1H, CHC=C), 12.48 s (1H, OH) (E1, 26%); 0.96 d (3H, CH**Me**), 2.30 s (3H, MeC=C), 3.72–3.82 m (1H, C**H**Me), 4.44 d (1H, CHC=C, J = 3 Hz), 11.18 s (1H, OH) (E2, 32%); 6.85–8.05 m (7H, H_{arom}). Found, %: C 55.04; H 3.61. $C_{20}H_{16}BrClO_4$. Calculated, %: C 55.13; H 3.70.

3-Acetyl-6-bromo-4-[2-(4-bromophenyl)-1-methyl-2-oxoethyl]chroman-2-one (Vc). Yield 67%, mp 146–148°C. ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 1.08 d (3H, CH**Me**), 2.20 s (3H, COMe), 3.25–4.00 m (1H, C**H**Me), 4.03 s and 4.20 s (2H, CHCH), 6.80–8.00 m (7H, H_{arom}); in DMSO-d_6–CCl_4 (1:3): 1.13 d (3H, CH**Me**), 2.25 s (3H, COMe), 3.70–3.80 m (1H, C**H**Me), 3.90 d (1H, C**H**CHCOMe), 3.95 s (1H, C**H**COMe) (K, 44%); 1.02 d (3H, CH**Me**), 2.14 s (3H, MeC=C), 3.70–3.80 m (1H, C**H**Me), 4.11 d (1H, CHC=C), 12.48 s (1H, OH) (E1, 24%); 0.95 d (3H, CH**Me**), 2.30 s (3H, MeC=C), 3.70–3.80 m (1H, C**H**Me), 4.43 d (1H, CHC=C, J = 3 Hz), 11.20 s (1H, OH) (E2, 32%); 6.85–8.05 m (7H, H_{arom}). Found, %: C 49.90; H 3.28; Br 33.08. $C_{20}H_{16}Br_2O_4$. Calculated, %: C 50.03; H 3.36; Br 33.28.

3-Acetyl-4-(1-benzoylpropyl)-6-bromochroman-2-one (Vd). Yield 42%, mp 115–118°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.80 t (3H, CH_2**Me**), 1.30–1.80 m (2H, C**H**$_2$Me), 3.55–3.75 m (1H, C**H**CH_2), 3.89 d (1H, C**H**CHCOMe), 3.90 s (1H, C**H**COMe) (K, 44%); 0.72 t (3H, CH_2**Me**), 1.30–1.80 m (2H, CH_2**Me**), 2.09 s (3H, MeC=C), 3.55–3.75 m (1H, C**H**CH_2), 4.04 d (1H, CHC=C), 12.27 s (1H, OH) (E1, 28%); 0.72 t (3H, CH_2**Me**), 1.30–1.80 m (2H, C**H**$_2$Me), 2.22 s (3H, MeC=C), 3.55–3.75 m (1H, C**H**CH_2), 4.37 d (1H, CHC=C, J = 4 Hz), 11.00 br.s (1H, OH) (E2, 28%); 6.80–8.00 m (8H, H_{arom}). Found, %: C 60.55; H 4.54; Br 19.06. $C_{21}H_{19}BrO_4$. Calculated, %: C 60.74; H 4.61; Br 19.24.

3-Benzoyl-6-bromo-4-[2-(4-bromophenyl)-1-methyl-2-oxoethyl]chroman-2-one (Ve). Yield 75%, mp 185–187°C. ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 1.08 d (3H, CH**Me**), 3.25–4.00 m (1H, C**H**Me), 3.66 s and 4.62 s (2H, CHCH), 6.90–8.10 m (13H, H_{arom}); in DMSO-d_6–CCl_4 (1:3): 1.21 d (3H, CH**Me**); 3.76 d (1H, C**H**CHCOPh); 3.90 m (1H, C**H**Me); 4.83 s (1H, C**H**COPh); 7.07 d, 7.26 s, and 7.45 d (3H, C_6H_3); 7.57 t, 7.67 t, and 7.69 d (5H, Ph); 7.98 d and 8.07 d (4H, 4-BrC_6H_4). Found, %: C 55.28; H 3.28; Br 29.31. $C_{25}H_{18}Br_2O_4$. Calculated, %: C 55.38; H 3.35; Br 29.47.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 04-03-9603).

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