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Reformatsky Reaction of Methyl α-Bromoisobutyrate with 2-Oxo-2*H*-benzo[*f*]chromene-3-carboxylic Acid Esters and *N*-Benzylamide

V. V. Shchepin, D. V. Fotin, and S. N. Shurov

Perm State University, ul. Bukireva, 15, Perm, 614600 Russia

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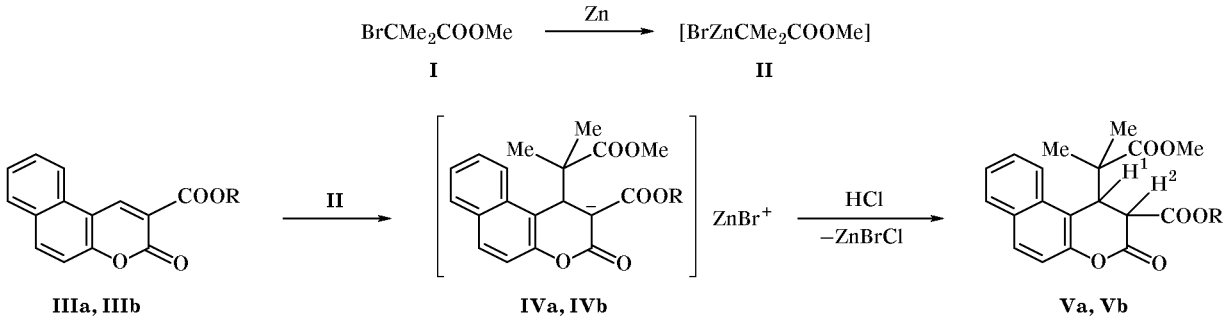
Abstract—Reformatsky reagent derived from methyl α-bromoisobutyrate reacts with methyl and ethyl 2-oxo-2*H*-benzo[*f*]chromene-3-carboxylates and *N*-benzyl-2-oxo-2*H*-benzo[*f*]chromene-3-carboxamide to afford the corresponding derivatives of 4-(1-methyl-1-methoxycarbonylethyl)-2-oxo-3,4-dihydro-2*H*-benzo[*f*]chromene-3-carboxylic acid as a single stereoisomer.

Reformatsky reagents are relatively mild nucleophiles which can be used to effect regioselective reactions with polyfunctional electrophilic substrates [1]. We were the first to examine the reaction of model Reformatsky reagent **II**, which was derived from methyl α-bromoisobutyrate (**I**), with alkyl 2-oxo-2*H*-benzo[*f*]chromene-3-carboxylates **IIIa** and **IIIb**. We found that organozinc compound **II** adds in a regio- and stereoselective fashion at the double bond of substrate **III**, yielding intermediate **IV** (Scheme 1). The subsequent hydrolysis of **IV** leads to formation of methyl and ethyl 4-(1-methoxycarbonyl-1-methylethyl)-2-oxo-3,4-dihydro-2*H*-benzo[*f*]chromene-3-carboxylates **Va** and **Vb**. Likewise, organozinc derivative **II** reacts with *N*-benzyl-2-oxo-2*H*-benzo[*f*]chromene-3-carboxamide (**VI**) to afford *N*-benzyl-4-(1-methoxycarbonyl-1-methylethyl)-2-oxo-3,4-dihydro-2*H*-benzo[*f*]chromene-3-carboxylate (**VII**) (Scheme 2).

The structure of compounds **Va**, **Vb**, and **VII** was proved by the data of elemental analysis and IR and ^{1}H NMR spectroscopy. Their IR spectra contained characteristic absorption bands in the regions 1730–1750 and 1780–1790 cm^{-1}, which belong to stretching vibrations of the ester and lactone carbonyl groups, respectively. Amide **VII** showed in the IR spectrum a broad carbonyl absorption band at 1650 cm^{-1} and amide NH absorption at 3330 cm^{-1}.

According to the ^{1}H NMR spectra, compounds **Va**, **Vb**, and **VII** are formed as a single stereoisomer. The spin–spin coupling constant between the protons in positions *3* (H^2) and *4* (H^1) is less than 1 Hz. The low value of $J(H^1,H^2)$ may be explained by the fact that the dihedral angle HC^3C^4H approaches 90° [2]. In order to verify this assumption and obtain an additional information on the product structure, we performed quantum-chemical calculations of the mole-

Scheme 1.



III–**V**, R = Me (**a**), Et (**b**).

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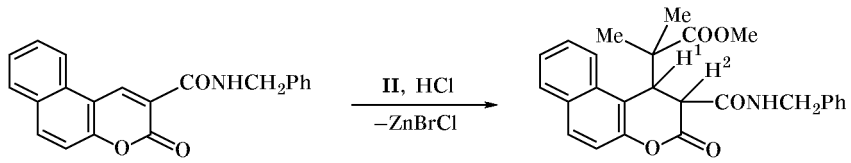
Scheme 2.

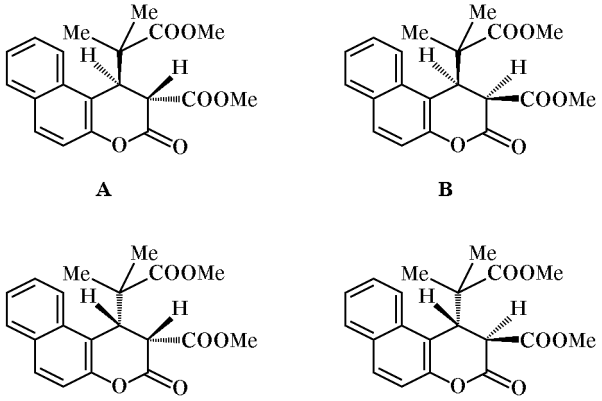


VI **VII**

cule of methyl 4-(1-methoxycarbonyl-1-methylethyl-2-oxo-3,4-dihydro-2*H*-benzo[*f*]chromene-3-carboxylate (**Va**) in terms of the SCF MO LCAO procedure using MNDO [3], AM1 [4], and MNDO–PM3 [5] approximations.

Theoretically, lactone **Va** can exist as four stereoisomers **A**–**D** with equatorial C^4-H and C^3-H bonds (**A**), equatorial C^4-H and axial C^3-H bonds (**B**), axial C^4-H and equatorial C^3-H bonds (**C**), and axial C^4-H and C^3-H bonds (**D**) (Scheme 3).

Scheme 3.



A **B**

C **D**

The isomers are characterized by the following enthalpies of formation (MNDO–MP3), kJ/mol: –852 (**A**), –827 (**B**), and –785 (**C**); after geometry optimization, stereoisomer **D** was transformed into **A**. According to the calculations, the naphthalene fragment is essentially planar, whereas the heterocyclic moiety adopts a flattened *boat* conformation. Comparison of the ΔH_f values listed above shows that isomer **A** is the most stable (regardless of the calculation procedure), while diastereoisomer **C** is the least stable. Bulky substituents at C^3 and C^4 in structure **A** occupy axial positions, so that they appear fairly distant from each other. The axial orientation of the CMe_2COOMe group on C^4 also ensures weaker interaction between the methyl groups and H^1 (C^4H). Stereoisomer **A** is characterized by the largest dihedral angle HC^3C^4H which actually tends to a value of 90° (especially in terms of the the MNDO and MNDO–PM3 approximations). Thus the results of calculations suggest that compounds **Va**, **Vb**, and **VII** have a structure like **A**.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer from samples dispersed in mineral oil. The ^1H NMR spectra of compounds **Va** and **VII** were recorded on an RYa-2310 instrument (60 MHz) using hexamethyldisiloxane as internal reference, and the spectrum of **Vb** was measured on a Bruker DRX-500 spectrometer (500 MHz) relative to tetramethylsilane.

Methyl 4-(1-methoxycarbonyl-1-methylethyl)-2-oxo-3,4-dihydro-2*H*-benzo[*f*]chromene-3-carboxylate (Va). Methyl α-bromoisobutyrate (**I**), 0.0012 mol, was added to a mixture of 2 g of zinc (prepared as fine turnings), 0.008 mol of methyl 2-oxo-2*H*-benzo[*f*]chromene-3-carboxylate (**IIIa**), 6 ml of diethyl ether, and 8 ml of benzene. The mixture was heated until a reaction started and, when the addition of **I** was complete, was kept for 30 min. It was then hydrolyzed with 5% hydrochloric acid and extracted with ether. The organic phase was dried over sodium sulfate and evaporated, and the product was recrystallized from methanol. Yield 76%, mp 111–112°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.10 s (6H, CMe_2), 3.35 s (3H, OMe), 3.45 s (3H, OMe), 4.30 s, 4.46 s (2H, CH), 7.00–8.20 m (6H). Found, %: C 67.32; H 5.58. $C_{20}H_{20}O_6$. Calculated, %: C 67.41; H 5.66.

Ethyl 4-(1-methoxycarbonyl-1-methylethyl)-2-oxo-3,4-dihydro-2*H*-benzo[*f*]chromene-3-carboxylate (Vb) was synthesized in a similar way using ethyl 2-oxo-2*H*-benzo[*f*]chromene-3-carboxylate (**IIIb**). Yield 70%, mp 86–87°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.86 t (3H, $OCH_2C\mathbf{H}_3$), 1.15 s and 1.17 s (6H, CMe_2), 3.62 s (3H, OMe), 3.92 q (2H, $OC\mathbf{H}_2$), 4.00 s and 4.50 s (2H, CH), 7.26–

8.03 m (6H). Found, %: C 68.00; H 5.92. $C_{21}H_{22}O_6$. Calculated, %: C 68.10; H 5.99.

***N*-Benzyl-4-(1-methoxycarbonyl-1-methylethyl)-2-oxo-3,4-dihydro-2*H*-benzo[*f*]chromene-3-carboxamide (VII)** was synthesized as decribed above for compound **Va** using amide **VI** as initial compound. Yield 52%, mp 178–179°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.10 s and 1.15 s (6H, CMe_2), 3.40 s (3H, OMe), 4.07 s and 4.40 s (2H, CH), ~4.08 d (NHC**H**$_2$), 6.70–8.10 m (11H, H_{arom}), 8.73 t (N**H**CH_2).

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