ISSN 1070-3632, Russian Journal of General Chemistry, 2006, Vol. 76, No. 7, pp. 1146–1149. © Pleiades Publishing, Inc., 2006.
Original Russian Text © V.V. Shchepin, N.F. Kirillov, M.I. Vakhrin, O.B. Bayanova, S.N. Shurov, P.S. Silaichev, 2006, published in Zhurnal Obshchei Khimii, 2006, Vol. 76, No. 7, pp. 1194–1197.

Reformatsky Reaction of Methyl 1-Bromocyclohexane-1-carboxylate with *N*-Aryl-2-oxochromene-3-carboxamides

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Received September 20, 2005

Abstract — Reformatsky reagent generated from methyl 1-bromocyclohexane-1-carboxylate reacted with *N*-aryl-2-oxochromene-3-carboxamides and *N*-aryl-6-bromo-2-oxochromene-3-carboxamides to give, depending on the conditions, the corresponding *N*-aryl-(6-bromo)-4-(1-methoxycarbonylcyclohexyl)-2-oxochroman-3-carboxamides or 3-aryl-(9-bromo)-1,1-pentamethylene-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-triones. The products were isolated as a single diastereoisomer.
DOI: 10.1134/S1070363206070255

We previously showed that classical Reformatsky reagents react with *N*-aryl-2-oxochromene-3-carboxamides to give substituted 4a,10b-dihydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-triones [1]. In the present work we studied reactions of organozinc reagent generated from methyl 1-bromocyclohexane-1-carboxylate with *N*-aryl-2-oxochromene-3-carboxamides and *N*-aryl-6-bromo-2-oxochromene-3-carboxamides **Ia**–**Ii**.

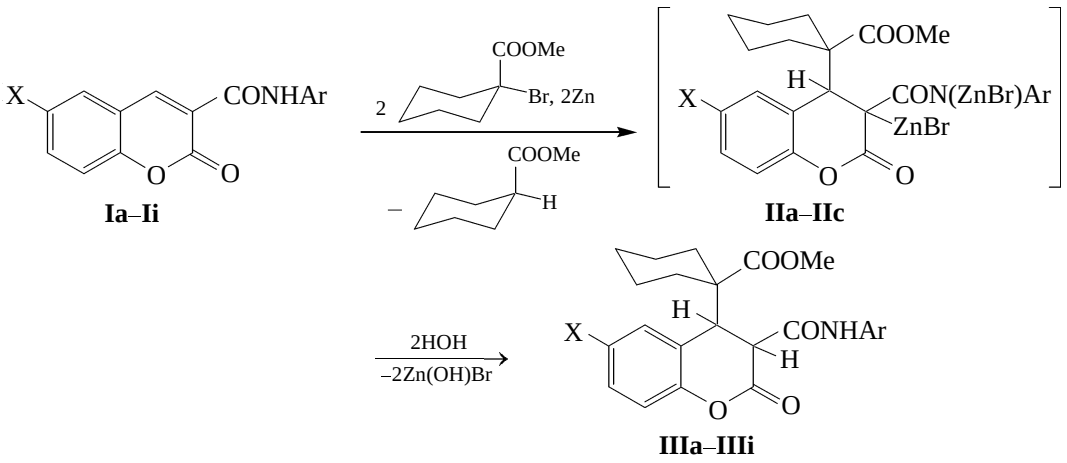
In the first stage, the organozinc compound adds at the double carbon–carbon bond of electrophilic substrates **Ia**–**Ii** to give intermediates **IIa**–**IIi** which do not undergo cyclization in benzene–ethyl acetate–HMPA (10 : 5 : 1); after hydrolysis, these intermediates are converted into *N*-aryl-4-(1-methoxycarbonylcyclohexyl)- and *N*-aryl-6-bpomo-4-(1-methoxycarbonylcyclohexyl)-2-oxochroman-3-carboxamides **IIIa**–**IIIi** (Scheme 1). The structure of the products was confirmed by their elemental compositions and spectral data. The IR spectra of **IIIa**–**IIIi** contain absorption bands belonging to stretching vibrations of the amide carbonyl group (1680–1690 cm^{-1}), ester carbonyl group (1720–1730 cm^{-1}), and lactone fragment (1740–1750 cm^{-1}), as well as of the N–H bond (3360–3370 cm^{-1}). According to the ^1H NMR data, compounds **IIIa**–**IIIi** were formed as a single diastereoisomer with respect to the dihydropyran ring. In the ^1H NMR spectra we observed two doublets at δ 3.34–3.76 and 4.00–4.27 ppm from the 4-H and 3-H protons with a coupling constant J of about 1.5 Hz.

Molecules **IIIa**–**IIIi** possess two chiral center, and they can exist as two diastereoisomers. To elucidate their steric structure we performed SCF MO LCAO MNDO–PM3 semiempirical calculations [2] of the enthalpies of formation (ΔH_f) and geometric parameters of two diastereoisomers A1 and A2 of compound **IIId**. In the more stable isomer A1, the benzene ring in the chroman fragment is planar. The C^4 atom lies in the same plane, while O^1 deviates from that plane by 0.16 Å, and the C^2 and C^3 atoms deviate from that plane by 0.54 and 0.75 Å, respectively. The cyclohexane ring adopts a *chair* conformation. The calculated dihedral angle HC^3C^4H (θ) in diastereoisomer A1 is 88.6°, and in A2, –57.9°. These values were used to calculate the vicinal coupling constant $J_{3,4}$(theor.) for each diastereoisomer by the Karplus equation [3] with the Bothner–By parameters [4]: $J_{3,4}$(theor.) = 2.0 (A1) and 4.3 Hz (A2). The experimental vicinal coupling constant $J_{3,4}$ for compound **IIId** (as well as for all other compounds of this series) is less than 2.0 Hz; therefore, they were assigned the structure of diastereoisomer A1.

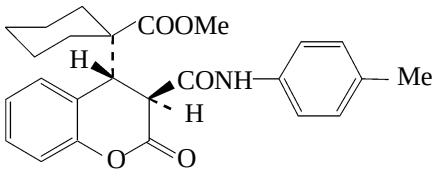
When the reaction with compounds **Ia**, **Id**, and **Ih** was carried out at elevated temperature (100°C; toluene–ethyl acetate–HMPA, 10 : 5 : 1), intramolecular cyclization via nucleophilic attack by the amide nitrogen atom on the ester carbonyl atom became possible. Hydrolysis of intermediates **IVa**, **IVd**, and **IVh** gave the final products, 3-aryl-1,1-pentamethylene-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-triones **Va** and **Vd** and 9-bromo-3-(4-methylphenyl)-1,1-pentamethylene-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-trione (**Vh**) (Scheme 2).

The IR spectra of compounds **Va**, **Vd**, and **Vh** contained absorption bands at 1685 and 1720 cm^{-1}

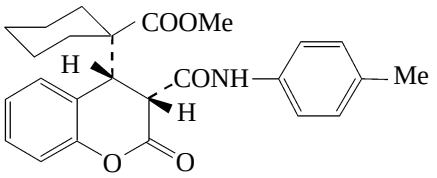
Scheme 1.



I–**III**, X = H, Ar = Ph (**a**), $PhCH_2$ (**b**), 4-BrC_6H_4 (**c**), 4-MeC_6H_4 (**d**), 4-$MeOC_6H_4$ (**e**); X = Br, Ar = Ph (**f**), 4-BrC_6H_4 (**g**), 4-MC6H4 (**h**), 4-$MeOC_6H_4$ (**i**).

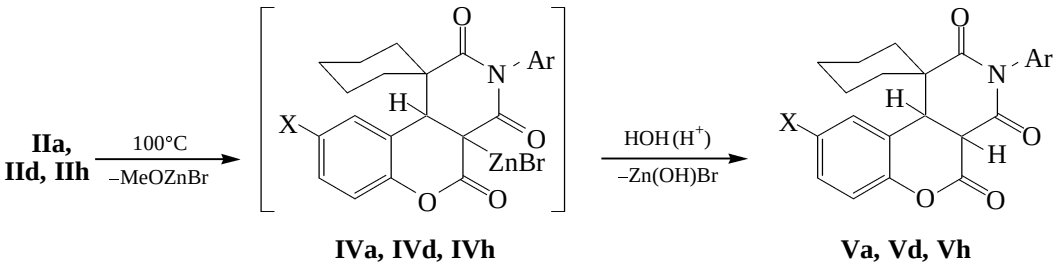


A1: 3*S*(*R*),4*R*(*S*)
ΔH_f –691.2 kJ mol^{-1}
θ 88.6°
$J_{3,4}$(theor.) 2.0 Hz



A2: 3*S*(*R*),4*R*(*S*)
ΔH_f –661.0 kJ mol^{-1}
θ –57.9°
$J_{3,4}$(theor.) 4.3 Hz

Scheme 2.

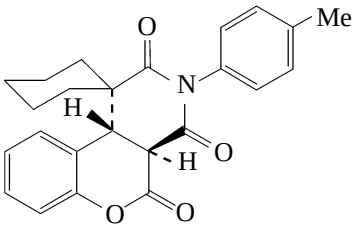


IV, V, X = H, Ar = Ph (**a**), 4-MeC_6H_4 (**d**); X = Br, Ar = 4-MeC_6H_4 (**h**).

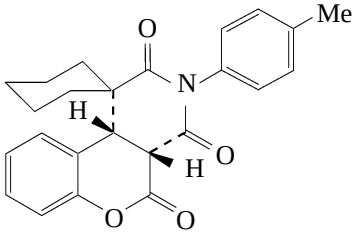
due to imide carbonyl groups and at 1750–1755 cm^{-1} due to lactone carbonyl. In the ^{1}H NMR spectra of **Va**, **Vd**, and **Vh** we observed only one set of signals, indicating formation of a single stereoisomer. The most characteristic was the presence of two doublets in the regions δ 3.55–3.92 and 3.98–4.58 ppm (*J* 6.5 Hz), which correspond to the 10b-H and 4a-H protons, respectively.

As above, the steric structure of products **Va**, **Vd**, and **Vh** was determined on the basis of the results of calculations of two possible diastereoisomers B1 and B2 of compound **Vd**.

Isomer B2 turned out to be more stable than B1. The benzene ring in the chroman fragment is planar, and the corresponding plane also includes the O^6 and C^{10b} atoms. The C^{4a} and C^5 atoms deviate from that plane by 0.80 and 0.24 Å, respectively. The piperidine fragment has a *chair* conformation flattened at the nitrogen atom. The cyclohexane ring exists in a *chair* conformation.



B1: 4a*S*(*R*),10b*R*(*S*)
ΔH_f –461.0 kJ mol^{-1}
θ 163.5°
$J_{4a,10b}$(theor.) 10.2 Hz



B2: 4a*S*(*R*),10b*R*(*S*)
ΔH_f –471.9 kJ mol^{-1}
θ 49.4°
$J_{4a,10b}$(theor.) 5.6 Hz

The dihedral angle $HC^{4a}C^{10b}H$ in diastereoisomer B2 is 49.4°, which corresponds to a vicinal coupling constant $^3J_{4a,10b}$ of 5.6 Hz. The same angle in diastereoisomer B1 is 163.5°, and the corresponding coupling constant was estimated at 10.2 Hz. The experimental coupling constants in the ^{1}H NMR spectra of **Va**, **Vd**, and **Vh** are equal to 6.5 Hz; therefore, these compounds were assigned structure B2.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer from samples dispersed in mineral oil. The 1H NMR spectra were measured on Tesla BS-567A (100 MHz; **IIIc**, **IIIe**–**IIIg**, **IIIi**, **Va**, **Vh**, $CDCl_3$; **IIIb**, **Vd**, DMSO-d_6; HMDS) and Bruker DRX instruments (500 MHz; **IIIa**, **IIId**, **IIIh**; DMSO-d_6, TMS). Quantum-chemical calculations were performed using MOPAC 7.0 software package [5].

***N*-Aryl-(6-bromo)-4-(1-methoxycarbonylcyclohexyl)-2-oxochroman-3-carboxamides IIIa–IIIi** *(general procedure).* Methyl 1-bromocyclohexane-1-carboxylate, 22 mmol, was added to a mixture of 2 g of zinc (prepared as fine turnings), 8 mmol of the corresponding *N*-aryl-(6-bromo)-2-oxochromene-3-carboxamide, 10 ml of benzene, 5 ml of ethyl acetate, and 1 ml of HMPA. The mixture was heated to initiate the reaction which then occurred spontaneously. When the exothermic reaction was over, the mixture was heated for 4 h under reflux, cooled, and treated with 5% acetic acid. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The extract was combined with the organic phase, washed with water, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized twice from toluene.

4-(1-Methoxycarbonylcyclohexyl)-2-oxo-*N*-phenylchroman-3-carboxamide (IIIa). Yield 62%, mp 189–190°C. IR spectrum, ν, cm^{-1}: 1680, 1720, 1740 (C=O); 3360 (NH). ^{1}H NMR spectrum, δ, ppm: 1.05–2.33 m [10H, $(CH_2)_5$], 3.37 d (1H, 4-H, *J* ~1.5 Hz), 3.52 s (3H, OMe), 4.26 d (1H, 3-H, *J* ~1.5 Hz), 7.02–7.42 m (9H, H_{arom}), 10.19 s (1H, NH). Found, %: C 70.68; H 6.01; N 3.33. $C_{24}H_{25}NO_5$. Calculated, %: C 70.74; H 6.18; N 3.44.

***N*-Benzyl-4-(1-methoxycarbonylcyclohexyl)-2-oxochroman-3-carboxamide (IIIb).** Yield 89%, mp 183–184°C. IR spectrum, ν, cm^{-1}: 1680, 1725, 1740 (C=O); 3365 (NH). ^{1}H NMR spectrum, δ, ppm: 0.86–2.29 m [10H, $(CH_2)_5$], 3.34 d (1H, 4-H, *J* ~1.5 Hz), 3.48 s (3H, OMe), 4.00 d (1H, 3-H, *J* ~1.5 Hz), 4.12 d (2H, CH_2Ph, *J* 5.5 Hz), 6.82–7.34 m (9H, H_{arom}), 8.70 br.s (1H, NH). Found, %: C 71.33; H 6.61; N 3.45. $C_{25}H_{27}NO_5$. Calculated, %: C 71.24; H 6.46; N 3.32.

***N*-(4-Bromophenyl)-4-(1-methoxycarbonylcyclohexyl)-2-oxochroman-3-carboxamide (IIIc).** Yield 72%, mp 200–201°C. IR spectrum, ν, cm^{-1}: 1685, 1720, 1740 (C=O); 3365 (NH). ^{1}H NMR spectrum, δ, ppm: 0.92–2.40 m [10H, $(CH_2)_5$], 3.52 s (3H, OMe), 3.71 d (1H, 4-H, *J* ~1.5 Hz), 4.13 d (1H, 3-H, *J* ~1.5 Hz), 6.70–7.52 m (8H, H_{arom}), 8.03 s (1H, NH). Found, %: C 59.46; H 5.05; Br 16.22; N 2.67. $C_{24}H_{24}BrNO_5$. Calculated, %: C 59.27; H 4.97; Br 16.43; N 2.88.

4-(1-Methoxycarbonylcyclohexyl)-***N*-(4-methylphenyl)-2-oxochroman-3-carboxamide (IIId).** Yield 90%, mp 183–184°C. IR spectrum, ν, cm^{-1}: 1680, 1725, 1740 (C=O); 3365 (NH). ^{1}H NMR spectrum, δ, ppm: 1.05–2.32 m [10H, $(CH_2)_5$], 2.22 s (3H, *Me*C_6H_4), 3.34 d (1H, 4-H, *J* ~1.5 Hz), 3.53 s (3H, OMe), 4.23 d (1H, 3-H, *J* ~1.5 Hz), 7.00–7.35 m (8H, H_{arom}), 10.11 s (1H, NH). Found, %: C 71.26; H 6.49; N 3.21. $C_{25}H_{27}NO_5$. Calculated, %: C 71.24; H 6.46; N 3.32.

4-(1-Methoxycarbonylcyclohexyl)-*N*-(4-methoxyphenyl)-2-oxochroman-3-carboxamide (IIIe). Yield

1725, 1745 (C=O); 3370 (NH). ^{1}H NMR spectrum, δ, ppm: 1.02–2.40 m [10H, $(CH_2)_5$], 3.61 s (3H, O*Me*), 3.69 s (3H, OMe), 3.76 d (1H, 4-H, *J* ~l.5 Hz), 4.08 d (1H, 3-H, *J* ~1.5 Hz), 6.60–7.30 m (8H, H_{arom}), 7.82 s (1H, NH). Found, %: C 68.81; H 6.05; N 3.35. $C_{25}H_{27}NO_6$. Calculated, %: C 68.63; H 6.22; N 3.20.

6-Bromo-4-(1-methoxycarbonylcyclohexyl)-2-oxo-*N*-phenylchroman-3-carboxamide (IIIf). Yield 34%, mp 230–232°C. IR spectrum, ν, cm^{-1}: 1685, 1720, 1740 (C=O); 3365 (NH). ^{1}H NMR spectrum, δ, ppm: 1.05–2.35 m [10H, $(CH_2)_5$], 3.62 s (3H, OMe), 3.75 d (1H, 4-H, *J* ~1.5 Hz), 4.16 d (1H, 3-H, *J* ~1.5 Hz), 6.89–7.52 m (8H, H_{arom}), 8.10 s (1H, NH). Found, %: C 59.11; H 5.06; Br 16.25; N 3.00. $C_{24}H_{24}BrNO_5$. Calculated, %: C 59.27; H 4.97; Br 16.43; N 2.88.

6-Bromo-*N*-(4-bromophenyl)-4-(1-methoxycarbonylcyclohexyl)-2-oxochroman-3-carboxamide (IIIg). Yield 38%, mp 211–212°C. IR spectrum, ν, cm^{-1}: 1685, 1720, 1745 (C=O); 3360 (NH). ^{1}H NMR spectrum, δ, ppm: 1.02–2.38 m [10H, $(CH_2)_5$], 3.61 s (3H, OMe), 3.68 d (1H, 4-H, *J* ~1.5 Hz), 4.10 d (1H, 3-H, *J* ~1.5 Hz), 6.73–7.40 m (7H, H_{arom}), 7.92 s (1H, NH). Found, %: C 50.87; H 3.98; Br 28.57; N 2.54. $C_{24}H_{23}Br_2NO_5$. Calculated, %: C 51.00; H 4.10; Br 28.27; N 2.48.

6-Bromo-4-(1-methoxycarbonylcyclohexyl)-*N*-(4-methylphenyl)-2-oxochroman-3-carboxamide (IIIh). Yield 43%, mp 197–198°C. IR spectrum, ν, cm^{-1}: 1690, 1725, 1740 (C=O); 3365 (NH). ^{1}H NMR spectrum, δ, ppm: 1.06–2.38 m [10H, $(CH_2)_5$]; 2.23 s (3H, MeC_6H_4); 3.39 d (1H, 4-H, *J* ~1.5 Hz); 3.52 s (3H, OMe); 4.27 d (1H, 3-H, *J* ~1.5 Hz); 7.02 d, 7.08 d, 7.31 d, 7.46 s, 7.50 d (7H, H_{arom}); 10.11 s (1H, NH). Found, %: C 59.88; H 5.32; Br 16.09; N 2.91. $C_{25}H_{26}BrNO_5$. Calculated, %: C 60.01; H 5.24; Br 15.97; N 2.80.

6-Bromo-4-(1-methoxycarbonylcyclohexyl)-*N*-(4-methoxyphenyl)-2-oxochroman-3-carboxamide (IIIi). Yield 58%, mp 156–157°C. IR spectrum, ν, cm^{-1}: 1690, 1730, 1750 (C=O); 3370 (NH). ^{1}H NMR spectrum, δ, ppm: 1.02–2.40 m [10H, $(CH_2)_5$], 3.61 s (3H, OMe), 3.69 s (3H, OMe), 3.76 d (1H, 4-H, *J* ~1.5 Hz), 4.08 d (1H, 3-H, *J* ~1.5 Hz), 6.60–7.30 m (8H, H_{arom}), 7.82 s (1H, NH). Found, %: C 58.31; H 4.92; Br 15.62; N 2.90. $C_{25}H_{26}BrNO_6$. Calculated, %: C 58.15; H 5.08; Br 15.47; N 2.71.

3-Aryl-(9-bromo)-1,1-pentamethylene-2,3,4,4a,-5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-triones Va, Vd, and Vh were synthesized according to the general procedure using toluene instead of benzene.

1,1-Pentamethylen-3-phenyl-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-trione (Va). Yield 58%, mp 223–224°C. IR spectrum, ν, cm^{-1}: 1685, 1720, 1755 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.96–2.40 m [10H, $(CH_2)_5$], 3.55 d (1H, 10b-H, *J* 6.5 Hz), 3.98 d (1H, 4a-H, *J* 6.5 Hz), 7.00–7.69 m (8H, H_{arom}). Found, %: C 73.72; H 5.49; N 3.85. $C_{23}H_{21}NO_4$. Calculated, %: C 73.58; H 5.64; N 3.73.

3-(4-Methylphenyl)-1,1-pentamethylene-2,3,4,-4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-trione (Vd). Yield 58%, mp 245–247°C. IR spectrum, ν, cm^{-1}: 1685, 1720, 1755 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.96–2.40 m [10H, $(CH_2)_5$], 2.33 s (3H, MeC_6H_4), 3.92 d (1H, 10b-H, *J* 6.5 Hz), 4.58 d (1H, 4a-H, *J* 6.5 Hz), 6.80–7.49 m (8H, H_{arom}). Found, %: C 73.88; H 5.89; N 3.81. $C_{24}H_{23}NO_4$. Calculated, %: C 74.02; H 5.95; N 3.60.

9-Bromo-3-(4-methylphenyl)-1,1-pentamethylene-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]-pyridine-2,4,5-trione (Vh). Yield 47%, mp 246–248°C. IR spectrum, ν, cm^{-1}: 1685, 1720, 1750 (C=O). ^{1}HNMR spectrum, δ, ppm: 1.30–2.40 m [10H, $(CH_2)_5$], 2.35 s (3H, MeC_6H_4), 3.69 d (1H, 10b-H, *J* 6.5 Hz), 4.01 d (1H, 4a-H, *J* 6.5 Hz), 6.75–7.54 m (7H, H_{arom}). Found, %: C 61.42; H 4.86; Br 16.89; N 3.15. $C_{24}H_{22}BrNO_4$. Calculated, %: C 61.55; H 4.73; Br 17.06; N 2.99.

ACKNOWLEDGMENTS

This study was performed under financial support by the Russian Foundation for Basic Research (project nos. 04-03-96036 and 04-03-97505).

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