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# Reaction of Organozinc Reagents Derived from Dialkyl 2,2-Dibromomalonates and Methyl 4,4-Dibromo-3-oxoalkanoates with 2-Oxochromene-3-carboxamides

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**Abstract** — Organozinc compounds obtained by treatment of dialkyl 2,2-dibromomalonates with zinc reacted with N-substituted 2-oxochromene-3-carboxamides to give dialkyl 1a-R-carbamoyl-2-oxo-1a,7b-dihydro-2*H*-cyclopropa[*c*]chromene-1,1-dicarboxylates or alkyl 2-R-1,3,4-trioxo-2,3-dihydro-1*H*,9b*H*-chromeno[3',4':1,3]-cyclopropa[1,2-*c*]pyrrole-9c-carboxylates. Reactions of N-substituted 2-oxochromene-3-carboxamides with zinc enolates derived from methyl 4,4-dibromo-3-oxoalkanoates led to the formation of the corresponding 9c-alkyl-2-R-2,3-dihydrochromeno[3',4':1,3]cyclopropa[1,2-*c*]pyrrole-1,3,4-triones.
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Organozinc reagents derived from dialkyl dibromomalonates were used previously in the cyclopropanation of alkyl 2-arylmethylidenemalonates [1]. The present work was aimed at synthesizing cyclopropane derivatives in which the three-membered ring is fused to a chromene fragment and linked to alkoxycarbonyl and amide groups. For this purpose we examined reactions of organozinc compounds **IIa** and **IIb** (prepared by treatment of dialkyl dibromomalonates **Ia** and **Ib**, respectively, with metallic zinc) with N-substituted 2-oxochromene-3-carboxamides **IIIa**–**IIId**. We found that these reactions follow Scheme 1.

In the first stage (diethyl ether–THF–HMPA, 7 : 10 : 1.5; 45–55°C), compounds **IIa** and **IIb** add at the $C^4$ atom of substrates **IIIa**–**IIIc** to form intermediates **IVa**–**IVd** which undergo intramolecular ring closure to compounds **Va**–**Vd**. Hydrolysis of the latter gives the corresponding cyclopropanation products, dialkyl 1a-R-carbamoyl-2-oxo-1a,7b-dihydro-2*H*-cyclopropa[*c*]chromene-1,1-dicarboxylates **VIa**–**VIc**.

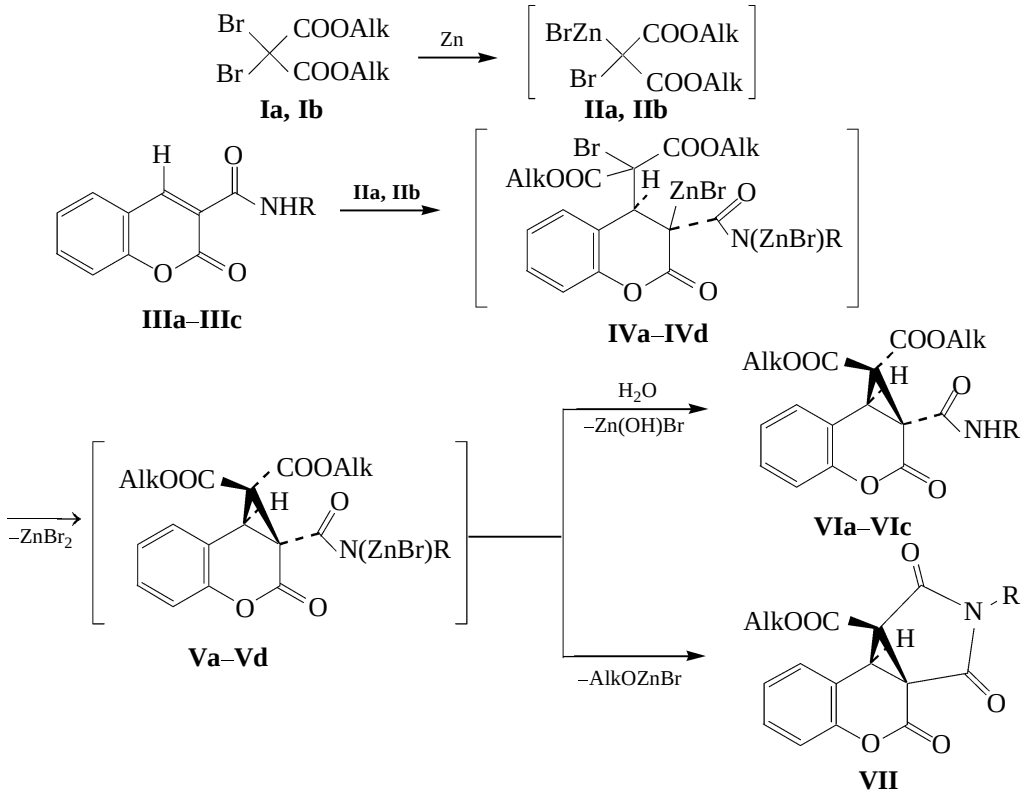
The structure of products **VIa**–**VIc** was confirmed by their analytical data and $^1$H NMR and IR spectra. The IR spectra of **VIa**–**VIc** contained a broad absorption band in the region 1680–1755 $cm^{-1}$, which corresponds to stretching vibrations of the amide, ester, and lactone carbonyl groups; N–H stretching vibrations appeared at 3410–3420 $cm^{-1}$. In the $^1$H NMR spectra of these compounds we observed a singlet at δ 4.15–4.21 ppm, which is typical of the 7b-H proton, and a doublet at δ ~6.20 ppm due to *ortho*-protons of the aromatic substituent in the amide group.

Addition of toluene to the reaction mixture increases the temperature to 85–90°C, thus promoting heterocyclization of intermediate **Vd** via interaction between the amide and ester groups which are located at the same side of the cyclopropane ring. As a result, the product is ethyl 2-(4-methoxyphenyl)-1,3,4-trioxo-2,3-dihydro-1*H*,9b*H*-chromeno[3',4' : 1,3]cyclopropa-[1,2-*c*]pyrrole-9c-carboxylate (**VII**). Compound **VII** shows in the IR spectrum absorption bands belonging to the imide (1705 and 1785 $cm^{-1}$), ester, and lactone carbonyl groups (~1755 $cm^{-1}$). Its $^1$H NMR spectrum contained a singlet at δ 4.59 ppm from the 9b-H proton and signals at δ 0.90 (t) and 3.94 ppm (q) from protons of the ester ethyl group.

We also prepared zinc enolates **IXa** and **IXb** from methyl 4,4-dibromo-3-oxobutanoate (**VIIIa**) and methyl 4,4-dibromo-3-oxopentanoate (**VIIIb**), respectively, and examined their reactions with N-substituted 2-oxochromene-3-carboxamides **IIIa**–**IIId**. The reactions were carried out in diethyl ether–ethyl acetate–tetrahydrofuran–HMPA (7 : 10 : 2 : 1.5); their mechanism is illustrated by Scheme 2.

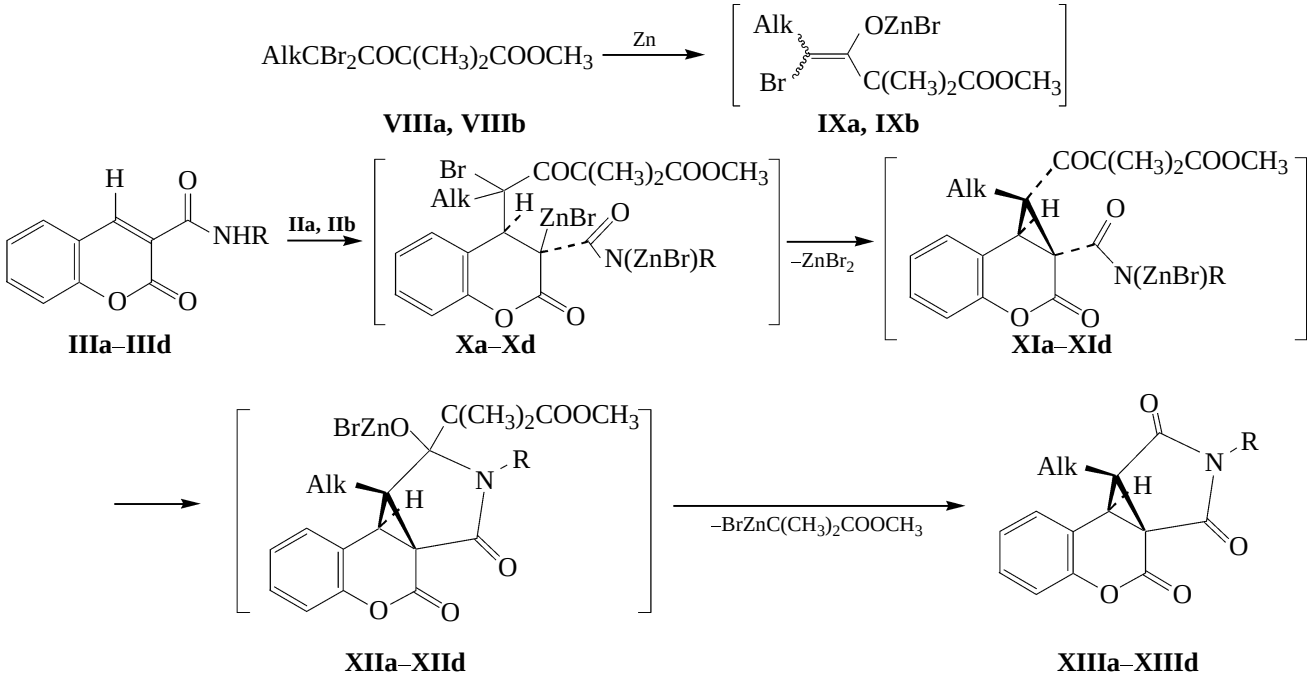
Zinc enolates **IXa** and **IXb** reacted with electrophilic substrates **IIIa**–**IIId** in a regioselective fashion to form intermediate adducts **Xa**–**Xd** which underwent stereoselective cyclization to give the corresponding cyclopropanation products **XIa**–**XId**. The

**Scheme 1.**




**I, II**, Alk = $CH_3$ (**a**), $CH_3CH_2$ (**b**); **III**, R = $C_6H_5$ (**a**), 4-$CH_3C_6H_4$ (**b**), 4-$CH_3OC_6H_4$ (**c**); **IV, V,** Alk = $CH_3$, R = 4-$MeOC_6H_4$ (**a**); Alk = $CH_3CH_2$, R = $C_6H_5$ (**b**), 4-$CH_3C_6H_4$ (**c**), 4-$MeOC_6H_4$ (**d**); **VI**, Alk = $CH_3$, R = 4-$MeOC_6H_4$ (**a**); Alk = $CH_2CH_3$, R = $C_6H_5$ (**b**), 4-$CH_3C_6H_4$ (**c**). **VII**, Alk = $CH_3CH_2$, R = 4-$MeOC_6H_4$.

**Scheme 2.**




**III**, R = $C_6H_{11}$ (**a**), $C_6H_5$ (**b**), $C_6H_5CH_2$ (**c**), 2-$CH_3C_6H_4$ (**d**); **VIII, IX**, Alk = $CH_3$ (**a**), $CH_2CH_3$ (**b**); **X**–**XIII**, Alk = $CH_3$; R = $C_6H_{11}$ (**a**), $C_6H_5$ (**b**), 2-$CH_3C_6H_4$ (**c**); Alk = $CH_3CH_2$, R = $C_6H_5CH_2$ (**d**).

amide and ketoester groups in the latter are located at the same side with respect to the three-membered ring plane; i.e., mutual arrangement of these groups is favorable for subsequent heterocyclization which may involve either ketone or ester moiety. The results showed that the attack by the amide group is directed at the ketone group with formation of intermediates **XIIa**–**XIId**. These intermediates are stabilized according to a pattern analogous to acid splitting of ethyl acetoacetate, and the final products are 9c-alkyl-2-R-2,3-dihydro-1*H*,9b*H*-chromeno[3',4' : 1,3]cyclopropa-[1,2-*c*]pyrrole-1,3,4-triones **XIIIa**–**XIIId**.

The IR spectra of compounds **XIIIa**–**XIIId** contained absorption bands typical of stretching vibrations of lactone (1745–1755 $cm^{-1}$) and imide carbonyl groups (1695–1715 and 1770–1800 $cm^{-1}$). The 9b-H proton appeared in the $^1H$ NMR spectra at δ 3.10–3.50 ppm, and signals from protons in the alkyl group on $C^{9c}$ were located at δ 1.21–1.28 ppm (**XIIIa**–**XIIIc**) or at δ 0.95 (t), 1.24 (m), and 1.94 ppm (m) (**XIIId**).

Compound **XIIIc** gives two sets of signals in the $^1H$ NMR spectrum. Presumably, this compound in solution exists as two conformers due to restricted rotation of the *o*-methylphenyl fragment with respect to the imide ring. The rotation of the *o*-tolyl fragment about the N–Ci bond was simulated by the reaction coordinate technique in terms of the MNDO-PM3 (SCF MO LCAO) approximation [2]; as reaction coordinate we used the dihedral angle θ. Two minima were revealed on the potential curve plotted in the $\Delta H_f$–θ coordinates. The energy barrier separating this minima was estimated at ~14.5 kcal $mol^{-1}$. Thus, the results of calculations confirmed our assumption that compound **XIIIc** exists as two fairly stable conformers.

## EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer from samples dispersed in mineral oil. The $^1H$ NMR spectra were measured on a Tesla BS-567A spectrometer (100 MHz) using HMDS as internal reference.

**Dialkyl 1a-R-carbamoyl-2-oxo-1a,7b-dihydro-2*H*-cyclopropa[*c*]chromene-1,1-dicarboxylates VIa**–**VIc** *(general procedure).* Dimethyl or diethyl 2,2-dibromomalonate, 0.024 mol, was added to a mixture of 2 g of metallic zinc (prepared as fine turnings), 7 ml of diethyl ether, and 10 ml of tetrahydrofuran. The mixture was heated to initiate reaction which then occurred spontaneously. When the exothermic reaction was complete, the mixture was heated for 5 min under reflux and cooled, the liquid phase was separated from excess zinc by decanting and was added to a mixture of 0.01 mol of N-substituted 2-oxochromene-3-carboxamide and 1.5 ml of HMPA, and the mixture was heated for 30–40 min under reflux. The mixture was cooled, hydrolyzed with 5% acetic acid, and extracted with benzene, the solvent was distilled off from the extract, and the residue was recrystallized from methanol.

**Dimethyl 1a-(4-methoxyphenylcarbamoyl)-2-oxo-1a,7b-dihydro-2*H*-cyclopropa[*c*]chromene-1,1-dicarboxylate (VIa).** Yield 46%, mp 186–187°C. IR spectrum, ν, $cm^{-1}$: 1680–1755, 3415. $^1H$ NMR spectrum, δ, ppm: 3.68 s (3H, $CH_3$), 3.85 s (6H, $2COOCH_3$), 4.21 s (1H, CH), 6.20–7.30 m (8H, $C_6H_4$, 4-$MeOC_6H_4$, and 1H, NH). Found, %: C 62.04; H 4.43. $C_{22}H_{19}NO_8$. Calculated, %: C 62.12; H 4.50.

**Diethyl 2-oxo-1a-phenylcarbamoyl-1a,7b-dihydro-2*H*-cyclopropa[*c*]chromene-1,1-dicarboxylate (VIb).** Yield 37%, mp 183–184°C. IR spectrum, ν, $cm^{-1}$: 1680–1750, 3410. $^1H$ NMR spectrum, δ, ppm: 1.31 t (6H, $2CH_3CH_2$), 4.20 s (1H, CH), 4.30 q (4H, $2CH_3CH_2$), 6.31–7.20 m (9H, $C_6H_4$, $C_6H_5$, and 1H, NH). Found, %: C 65.16; H 4.94. $C_{23}H_{21}NO_7$. Calculated, %: C 65.24; H 5.00.

**Diethyl 1a-(4-methylphenylcarbamoyl)-2-oxo-1a,7b-dihydro-2*H*-cyclopropa[*c*]chromene-1,1-dicarboxylate (VIc).** Yield 48%, mp 171–172°C. IR spectrum, ν, $cm^{-1}$: 1680–1755, 3420. $^1H$ NMR spectrum, δ, ppm: 1.25 t (6H, $2CH_3CH_2$), 2.19 s (3H, $CH_3$), 4.15 s (1H, CH), 4.22 q (4H, $2CH_3CH_2$), 6.15–7.10 m (8H, $C_6H_4$, 4-$MeC_6H_4$, and 1H, NH). Found, %: C 65.82; H 5.22. $C_{24}H_{23}NO_7$. Calculated, %: C 65.90; H 5.30.

**Ethyl 2-(4-methoxyphenyl)-1,3,4-trioxo-2,3-dihydro-1*H*,9b*H*-chromeno[3',4' : 1,3]cyclopropa[1,2-*c*]pyrrole-9c-carboxylate (VII)** was synthesized as described above for compounds **VIa**–**VIc**, but in the second step 10 ml of toluene was added. Yield 43%, mp 229–230°C. IR spectrum, ν, $cm^{-1}$: 1705, 1755, 1785. $^1H$ NMR spectrum, δ, ppm: 0.90 t (3H, $CH_3 \cdot CH_2$), 3.78 s (1H, $OCH_3$), 3.94 q (2H, $CH_3CH_2$), 4.59 s (1H, CH), 6.92–7.53 m (8H, $C_6H_4$, 4-$MeO \cdot C_6H_4$). Found, %: S 64.80; H 4.16. $C_{22}H_{17}NO_7$. Calculated, %: C 64.86; H 4.21.

**2-R-9c-Alkyl-2,3-dihydro-1*H*,9b*H*-chromeno-[3',4' : 1,3]cyclopropa[1,2-*c*]pyrrole-1,3,4-triones XIIIa**–**XIIId** *(general procedure).* Methyl 4,4-dibromo-2,2-dimethyl-3-oxopentanoate or methyl 4,4-dibromo-2,2-dimethyl-3-oxohexanoate, 0.024 mol, was added to a mixture of 2 g of metallic zinc (prepared as fine turnings), 7 ml of diethyl ether, 10 ml of ethyl acetate, and 2 ml of THF. The mixture was

heated to initiate reaction which then occurred spontaneously. When the exothermic reaction was complete, the mixture was heated for 5 min under reflux and cooled, the liquid phase was separated from excess zinc by decanting and was added to a mixture of 0.01 mol of N-substituted 2-oxochromene-3-carboxamide and 1.5 ml of HMPA, and the mixture was heated for 30–40 min under reflux. The mixture was cooled, hydrolyzed with 5% acetic acid, and extracted with benzene, the solvent was distilled off from the extract, and the residue was recrystallized from methanol.

**2-Cyclohexyl-9c-methyl-2,3-dihydro-1*H*,9b*H*-chromeno[3',4' : 1,3]cyclopropa[1,2-*c*]pyrrole-1,3,4-trione (XIIIa).** Yield 34%, mp 234–236°C. IR spectrum, ν, $cm^{-1}$: 1705, 1750, 1785. $^1H$ NMR spectrum, δ, ppm: 1.24 s (3H, $CH_3$), 1.35–2.13 m (10H, $C_6H_{11}$), 3.14 s (1H, CH), 3.14–3.97 m (1H, $C_6H_{11}$), 6.96–7.28 m (4H, $C_6H_4$). Found, %: C 70.08; H 5.81. $C_{19}H_{19}NO_4$. Calculated, %: C 70.14; H 5.89.

**9c-Methyl-2-phenyl-2,3-dihydro-1*H*,9b*H*-chromeno[3',4' : 1,3]cyclopropa[1,2-*c*]pyrrole-1,3,4-trione (XIIIb).** Yield 32%, mp 242–244°C. IR spectrum, ν, $cm^{-1}$: 1705, 1750, 1785. $^1H$ NMR spectrum, δ, ppm: 1.33 s (3H, $CH_3$), 3.49 s (1H, CH), 6.92–7.42 m (9H, $C_6H_4$, $C_6H_5$). Found, %: C 71.41; H 4.03. $C_{19}H_{13}NO_4$. Calculated, %: C 71.47; H 4.10.

**9c-Methyl-2-(2-methylphenyl)-2,3-dihydro-1*H*,9b*H*-chromeno[3',4' : 1,3]cyclopropa[1,2-*c*]-pyrrole-1,3,4-trione (XIIIc).** Yield 34%, mp 273–275°C. IR spectrum, ν, $cm^{-1}$: 1705, 1750, 1785. $^1H$ NMR spectrum, δ, ppm: 1.23 s (3H, $CH_3$), 2.11 s (3H, 2-C$H_3$C$_6$H$_4$), 4.08 s (1H, CH), 7.05–7.65 m (8H, $C_6H_4$, 2-$CH_3C_6H_4$); rotational isomer: 2.14 s (3H, 2-C$H_3$C$_6$H$_4$), 4.43 s (1H, CH). Found, %: C 71.97; H 4.46. $C_{20}H_{15}NO_4$. Calculated, %: C 72.06; H 4.54.

**2-Benzyl-9c-ethyl-2,3-dihydro-1*H*,9b*H*-chromeno[3',4' : 1,3]cyclopropa[1,2-*c*]pyrrole-1,3,4-trione (XIIId).** Yield 46%, mp 172–174°C. IR spectrum, ν, $cm^{-1}$: 1700 1750, 1780. $^1H$ NMR spectrum, δ, ppm: 0.95 t (3H, C$H_3$CH$_2$), 1.24 m and 1.94 m (2H, CH$_3$C$H_2$), 3.13 s (1H, CH), 4.57 s (2H, $CH_2$), 6.90–7.37 m (9H, $C_6H_4$, $C_6H_5$). Found, %: C 72.52; H 4.88. $C_{21}N_{17}NO_4$. Calculated, %: C 72.61; H 4.93.

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