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Reaction of the Zinc Enolate Derived from 1,1-Dibromo-3,3-dimethylbutan-2-one with 3-Aryl-2-cyanopropenoic Acid Amides and Esters and 2-Oxochromene-3-carboxamides

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Abstract—Zinc enolate derived from 1,1-dibromo-3,3-dimethylbutan-2-one reacts with 3-aryl-2-cyanoprop-2-enamides and aryl 3-aryl-2-cyanoprop-2-enoates to give the corresponding derivatives of 3-aryl-2-(2,2-dimethylpropanoyl)-1-cyanocyclopropane-1-carboxylic acid as a single stereoisomer with *cis* arrangement of the hydrogen atoms at the cyclopropane ring. The reactions of the same zinc enolate with 3-morpholinocarbonyl-2*H*-chromen-2-one and 2-morpholinocarbonyl-3*H*-benzo[*f*]chromen-3-one lead to formation of 1-(2,2-dimethylpropanoyl)-1a-morpholinocarbonyl-1a,7b-dihydrocyclopropa[*c*]chromen-2-one and 1-(2,2-dimethylpropanoyl)-1a-morpholinocarbonyl-1a,9c-dihydrobenzo[*f*]cyclopropa[*c*]chromen-2-one, respectively as a single stereoisomer.

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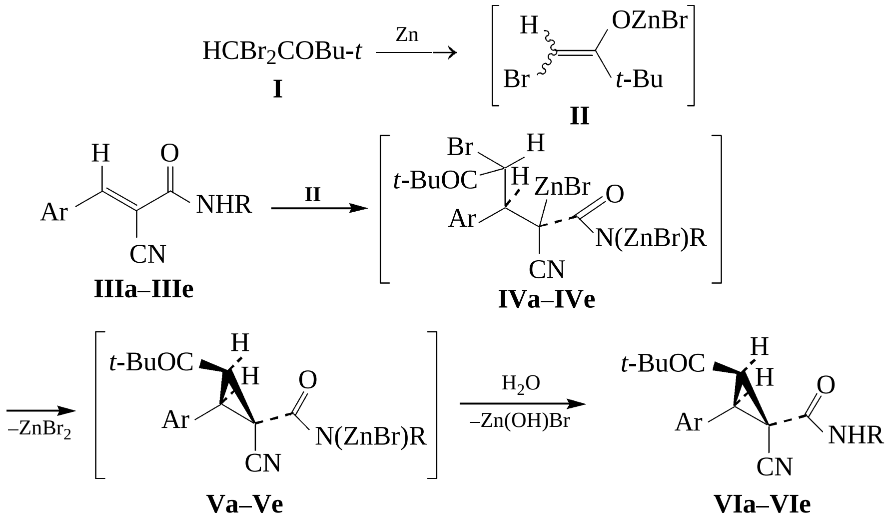
We previously found that successful cyclopropanation of 2-arylmethylidenemalonic and 2-oxo-2*H*-chromen-3-carboxylic acid derivatives with simultaneous introduction of an aroyl group into the three-membered ring is possible with the use of bromine-containing zinc enolates derived from 1-aryl-2,2-dibromoalkan-1-ones [1, 2].

With a view to obtain new classes of cyclopropane derivatives having a bulky pivaloyl group instead of aroyl we examined reactions of zinc enolate **II** [generated by treatment of 1,1-dibromo-3,3-dimethylbutan-2-one (**I**) with zinc dust] with 3-aryl-2-cyanoprop-2-enamides **IIIa**–**IIIe**. Zinc enolate **II** showed a high reactivity toward electrophilic substrates **IIIa**–**IIIe**, and the reactions followed Scheme 1.

Scheme 1.



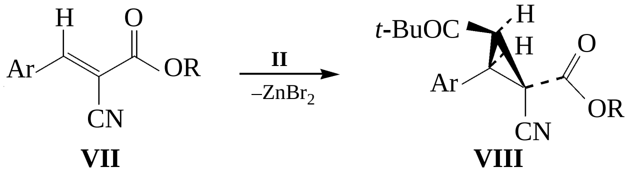
III–**VI**, Ar = Ph, R = $PhCH_2$ (**a**), 4-MeC_6H_4 (**b**), 2-MeC_6H_4 (**c**); Ar = 4-BrC_6H_4, R = $PhCH_2$ (**d**), *cyclo*-C_6H_{11} (**e**).

Initially, compounds **IIIa**–**IIIe** react with enolate **II** to give the corresponding salts which, despite their reduced electrophilicity, take up molecule **II** at C^3 with high regioselectivity. Adducts **IVa**–**IVe** thus formed undergo spontaneous cyclization to intermediates **Va**–**Ve**, and hydrolysis of the latter yields the final products, Nsubstituted 3-aryl-1-cyano-2-(2,2-dimethylpropanoyl)cyclopropane-1-carboxamides **VIa**–**VIe**.

The structure of compounds **IVa**–**IVe** was proved by the analytical data and ^{1}H NMR and IR spectra. The IR spectra of **VIa**–**VIe** characteristically contained absorption bands belonging to stretching vibrations of the amide and ketone carbonyl groups (1660–1705 cm^{-1}) and NH bonds (3325–3390 cm^{-1}). In the ^{1}H NMR spectra of **VIa**–**VIe**, signals from protons in the *tert*-butyl group (δ 1.08–1.14 ppm) and methine protons (δ 3.31–3.47 ppm) were observed; the presence of only one set of signals indicated that these compounds were formed as a single stereoisomer. In keeping with published data, spin–spin coupling constants for vicinal protons in the cyclopropane ring of analogous compounds differ considerably for the *cis* and *trans* isomers, J_{cis} = 9.4–9.8, J_{trans} = 5.1–5.5 Hz [3]. In the ^{1}H NMR spectrum of **VIb** in DMSO-d_6 the coupling constant between the cyclopropane ring protons was J_{HH} = 10.2 Hz. Therefore, the pivaloyl and amide group in molecule **VIb** are located at opposite sides of the cyclopropane ring plane. As concerns mutual arrangement of the aryl substituent and the amide group, their *trans* configuration inherent to initial amides **IIIa**–**IIIe** is likely to be conserved in products **VIa**–**VIe**, which is consistent with the concept implying that bulky groups should be maximally distant from each other.

We then examined the reaction of zinc enolate **II** with 4-bromophenyl 2-cyano-3-phenylprop-2-enoate (**VII**). The reaction followed an analogous scheme and afforded 4-bromophenyl 1-cyano-2-(2,2-dimethylpropanoyl)-3-phenylcyclopropane-1-carboxylate (**VIII**) (Scheme 2).

Scheme 2.



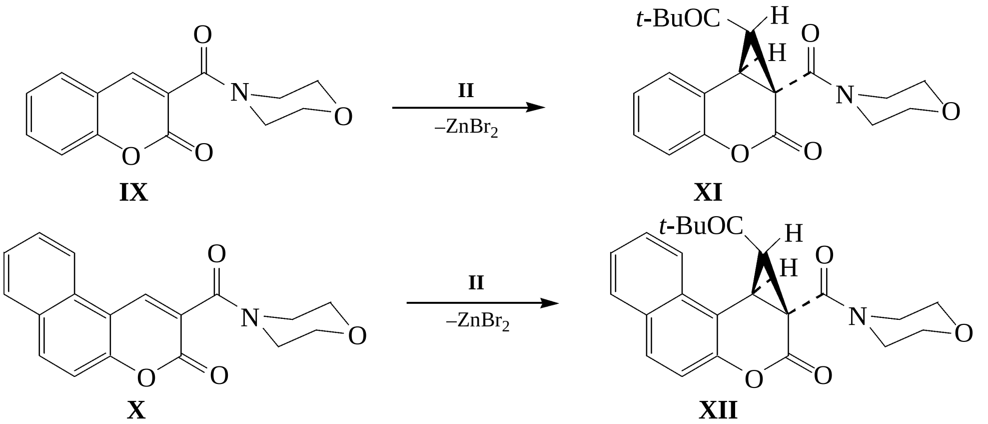
VII **VIII**

VII, VIII, Ar = Ph, R = 4-BrC$_6$H$_4$.

The structure of product **VIII** was proved by the analytical data and ^{1}H NMR and IR spectra. The IR spectrum of **VIII** characteristically contained absorption bands due to the ketone and ester carbonyl groups (1700 and 1750 cm^{-1}, respectively). Compound **VIII** displayed only one set of signals in the ^{1}H NMR spectrum, and the coupling constant $J_{2,3}$ was equal to 10.8 Hz. These data suggest that compound **VIII** is formed as a single stereoisomer with the same configuration as in **VIa**–**VIe**.

With a view to obtain cyclopropanated heterocycles, zinc enolate **II** was brought into reactions with 2-oxochromene-3-carboxylic acid morpholide (**IX**) and 3-oxobenzo[*f*]chromene-2-carboxylic acid morpholide (**X**). As in the above reactions, the attack by zinc enolate **II** was directed at the electron-deficient double-bonded carbon atom, and the products were the corresponding cyclopropane derivatives, 1-(2,2-dimethylpropanoyl)-1a-morpholinocarbonyl-1a,7b-dihydrocyclopropa[*c*]chromen-2-one (**XI**) and 1-(2,2-dimethylpropanoyl)-1a-morpholinocarbonyl-1a,9c-dihydrobenzo[*f*]cyclopropa[*c*]chromen-2-one (**XII**) (Scheme 3).

Scheme 3.



Compounds **XI** and **XII** showed in the IR spectra absorption bands typical of amide (1655–1675 cm^{-1}), ketone (1710–1715 cm^{-1}), and lactone carbonyl groups (1740–1760 cm^{-1}). Only one set of signals was observed in the ^{1}H NMR spectra of these compounds, indicating that they were formed as a single stereoisomer. However, the vicinal coupling constant (J_{HH} = 7.5 Hz) did not allow us to unambiguously determine configuration of the substituents at the three-membered ring.

EXPERIMENTAL

The IR spectra were measured on a UR-20 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra of compounds **VIa**–**VIe**, **VIII**, **XI**, and **XII** were recorded on a Tesla BS-576A spectrometer (100 MHz) from solutions in $CDCl_3$. The ^{1}H NMR spectra of **VIb**, **VIII**, **XI**, and **XII** were also obtained from solutions in DMSO-d_6 on a Varian Mercury Plus-300 instrument (300 MHz) using HMDS as internal reference.

N-Substituted 3-aryl-1-cyano-2-(2,2-dimethylpropanoyl)cyclopropane-1-carboxamides VIa–**VIe** *(general procedure).* 1,1-Dibromo-3,3-dimethylbutan-2-one, 0.025 mol, was added to a mixture of 4 g of zinc (prepared as fine turnings), 7 ml of diethyl ether, and 10 ml of ethyl acetate. The mixture was heated to initiate a reaction which then occurred spontaneously. When the reaction was complete, the mixture was heated for 15 min under reflux and cooled, and the solution was separated from the remaining zinc turnings by decanting. Compound **IIIa**–**IIIe**, 0.01 mol, was added to the solution, and the mixture was heated for 30–40 min under reflux, cooled, treated with 5% acetic acid, and extracted with benzene. The solvent was distilled off from the extract, and the residue was recrystallized from ethyl acetate or methanol.

***N*-Benzyl-1-cyano-2-(2,2-dimethylpropanoyl)-3-phenylcyclopropane-1-carboxamide (VIa).** Yield 64%, mp 126–128°C. IR spectrum, ν, cm^{-1}: 1680, 3390. ^{1}H NMR spectrum, δ, ppm: 1.14 s (9H, $3CH_3$), 3.43 s (2H, 2CH), 4.43 d (2H, CH_2Ph), 6.95–7.22 m (11H, C_6H_5, NH). Found, %: C 76.52; H 6.62; N 7.72. $C_{23}H_{24}N_2O_2$. Calculated, %: C 76.64; H 6.71; N 7.77.

1-Cyano-2-(2,2-dimethylpropanoyl)-*N*-(4-methylphenyl)-3-phenylcyclopropane-1-carboxamide (VIb). Yield 61%, mp 194–196°C. IR spectrum, ν, cm^{-1}: 1675, 3325. ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 1.12 s (9H, $3CH_3$), 2.25 s (3H, CH_3), 3.47 s (2H, 2CH), 6.91–7.31 m (9H, C_6H_5, $CH_3C_6H_4$), 8.21 s (1H, NH); in DMSO-d6: 1.11 s (9H, $3CH_3$); 2.22 s (3H, CH_3); 3.55 d.d (2H, 2CH, *J* = 10.2 Hz); 7.10 d, 7.20–7.40 m, and 7.47 d (9H, C_6H_5, 4-$CH_3C_6H_4$); 10.40 s (1H, NH). Found, %: C 76.55; H 6.60; N 7.71. $C_{23}H_{24}N_2O_2$. Calculated, %: C 76.64; H 6.71; N 7.77.

1-Cyano-2-(2,2-dimethylpropanoyl)-*N*-(2-methylphenyl)-3-phenylcyclopropane-1-carboxamide (VIc). Yield 73%, mp 162–162°C. IR spectrum, ν, cm^{-1}: 1680, 1705, 3330. ^{1}H NMR spectrum, δ, ppm: 1.12 s (9H, $3CH_3$), 2.26 s (3H, CH_3), 3.45 s (2H, 2CH), 6.90–7.21 m (9H, C_6H_5, $CH_3C_6H_4$), 8.26 s (1H, NH). Found, %: C 76.53; H 6.64; N 7.69. $C_{23}H_{24}N_2O_2$. Calculated, %: C 76.64; H 6.71; N 7.77.

***N*-Benzyl-3-(4-bromophenyl)-1-cyano-2-(2,2-dimethylpropanoyl)cyclopropane-1-carboxamide (VId).** Yield 62%, mp 137–138°C. IR spectrum, ν, cm^{-1}: 1675, 1680, 2225, 3390. ^{1}H NMR spectrum, δ, ppm: 1.10 s (9H, $3CH_3$), 3.38 s (2H, 2CH), 4.39 d (2H, CH_2Ph), 6.85–7.34 m (10H, C_6H_5, BrC_6H_4, NH). Found, %: C 62.77; H 5.21; N 6.32. $C_{23}H_{23}BrN_2O_2$. Calculated, %: C 62.88; H 5.28; N 6.38.

3-(4-Bromophenyl)-1-cyano-*N*-cyclohexyl-2-(2,2-dimethylpropanoyl)cyclopropane-1-carboxamide (VIe). Yield 59%, mp 214–216°C. IR spectrum, ν, cm^{-1}: 1660, 3355. ^{1}H NMR spectrum, δ, ppm: 1.08 s (9H, $3CH_3$), 1.05–2.00 m (10H, C_6H_{11}), 3.31 s (2H, 2CH), 3.71 m (1H, C_6H_{11}), 6.41 d (1H, NH), 6.97 d and 7.26 d (4H, BrC_6H_4). Found, %: C 61.19; H 6.20; N 6.42. $C_{22}H_{27}BrN_2O_2$. Calculated, %: C 61.26; H 6.31; N 6.49.

4-Bromophenyl 1-cyano-2-(2,2-dimethylpropanoyl)-3-phenylcyclopropane-1-carboxylate (VIII) was synthesized by the procedure described above for the synthesis of compounds **VIa**–**VIe** using 0.015 mol of 1,1-dibromo-3,3-dimethylbutan-2-one for the preparation of zinc enolate and 4-bromophenyl 2-cyano-3-phenylprop-2-enoate as substrate. Yield 74%, mp 113–115°C. IR spectrum, ν, cm^{-1}: 1700, 1750. ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 1.15 s (9H, $3CH_3$), 3.44 s (2H, 2CH), 6.95 d and 7.10–7.43 m (9H, BrC_6H_4, C_6H_5); in DMSO-d_6: 1.17 s (9H, $3CH_3$), 3.75 d.d (2H, 2CH, *J* = 10.8 Hz), 7.30–7.68 m (9H, BrC_6H_4, C_6H_5). Found, %: C 61.89; H 4.65; N 3.21. $C_{22}H_{20}BrNO_3$. Calculated, %: C 61.98; H 4.73; N 3.29.

1-(2,2-Dimethylpropanoyl)-1a-morpholinocarbonyl-1a,7b-dihydrocyclopropa[*c*]chromen-2-one (XI) and 1-(2,2-dimethylpropanoyl)-1a-morpholinocarbonyl-1a,9c-dihydrobenzo[*f*]cyclopropa[*c*]chromen-2-one (XII) were synthesized as described above for compound **VIII** using as substrate 3-morpholinocarbonyl-2*H*-chromen-2-one (**IX**) and 2-morpholinocarbonyl-3*H*-benzo[*f*]chromen-3-one (**X**), respectively.

1-(2,2-Dimethylpropanoyl)-1a-morpholinocarbonyl-1a,7b-dihydrocyclopropa[*c*]chromen-2-one (XI). Yield 61%, mp 150–151°C. IR spectrum, ν, cm^{-1}: 1655, 1715, 1740. ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 1.24 s (9H, *t*-Bu), 3.15 d (1H, CH, J = 7.4 Hz), 3.32–3.63 m (8H, C_4H_8NO), 3.84 d (1H, CH, J = 7.4 Hz), 6.58–7.10 m (4H, C_6H_4); in DMSO-d_6: 1.21 s (9H, *t*-Bu); 3.32 d (1H, CH, J = 7.5 Hz); 3.31–3.68 m (8H, C_4H_8NO); 3.46 d (1H, CH, J = 7.5 Hz); 6.73 t, 6.79 d, 6.98 d, and 7.05 t (4H, C_6H_4). Found, %: C 67.12; H 6.38; N 3.83. $C_{20}H_{23}NO_5$. Calculated, %: C 67.21; H 6.49; N 3.92.

1-(2,2-Dimethylpropanoyl)-1a-morpholinocarbonyl-1a,9c-dihydrobenzo[*f*]cyclopropa[*c*]chromen-2-one (XII). Yield 49%, mp 237–238°C. IR spectrum, ν, cm^{-1}: 1675, 1710, 1760. ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 1.14 s (9H, *t*-Bu), 2.71 d (1H, CH, J = 4.8 Hz), 3.00–3.90 m (8H, C_4H_8NO, and 1H, CH), 7.00–7.90 m (6H, $C_{10}H_6$); in DMSO-d_6: 1.14 s (9H, *t*-Bu); 3.13 d (1H, CH, J = 7.5 Hz); 3.05–3.80 m (8H, C_4H_8NO); 3.43 d (1H, CH, J = 7.5 Hz); 7.35 d, 7.56 t, 7.67 t, and 7.95–8.07 m (6H, $C_{10}H_6$). Found, %: C 70.63; H 6.11; N 3.36. $C_{24}H_{25}NO_5$. Calculated, %: C 70.74; H 6.18; N 3.44.

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