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Reactions of Organozinc Reagents Derived from Dialkyl 2,2-Dibromomalonates with 3-Aryl-2-cyanoprop-2-enamides

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Abstract—Organozinc compounds obtained by treatment of dialkyl 2,2-dibromomalonates with metallic zinc reacted with N-substituted 3-aryl-2-cyanoprop-2-enoic acid amides to give alkyl 3-R-6-aryl-5-cyano-2,4-dioxo-3-azabicyclo[3.1.0]hexane-1-carboxamides as a single stereoisomer.
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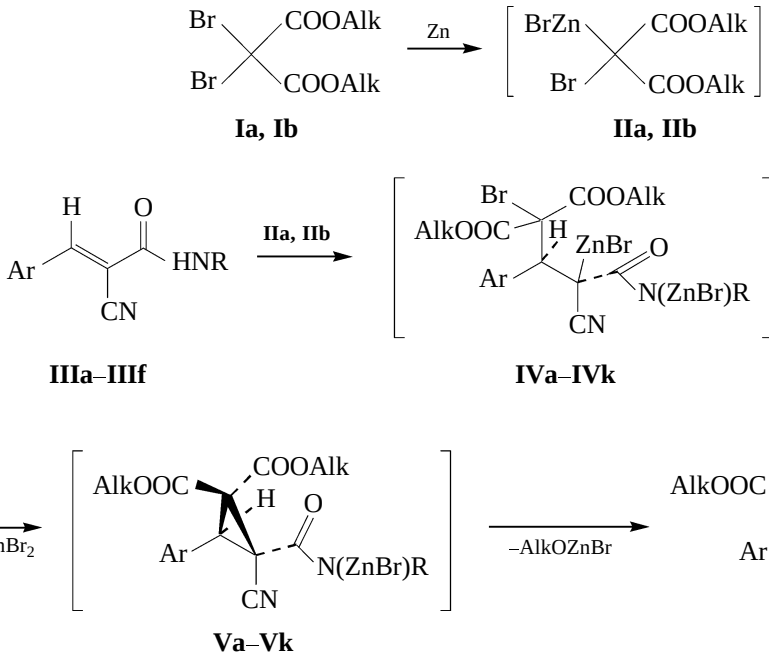
Gaudemar-Bordone and Gaudemar [1] previously reported on the cyclopropanation of dialkyl 2-alkylidenemalonates with organozinc reagents derived from dialkyl 2,2-dibromomalonates. In the present work we tried to obtain cyclopropane derivatives containing alkoxycarbonyl, amide, and cyano groups at the three-membered ring by reactions of organozinc compounds **IIa** and **IIb** with N-substituted 3-aryl-2-cyanoprop-2-enamides **IIIa**–**IIIf**. Organozinc reagents **IIa** and **IIb** were prepared by treatment of dialkyl 2,2-dibromomalonates **Ia** and **Ib**, respectively, with metallic zinc. The reactions followed the scheme shown below.



I, II, Alk = CH_3 (**a**), CH_3CH_2 (**b**); **III**, R = CH_2Ph, Ar = C_6H_5 (**a**), 4-ClC_6H_4 (**b**), 4-BrC_6H_4 (**c**); R = C_6H_5, Ar = C_6H_5 (**d**); R = 4-$CH_3C_6H_4$, Ar = C_6H_5 (**e**); R = C_6H_{11}, Ar = 4-BrC_6H_4 (**f**); **IV**–**VI**, R = CH_2Ph, Ar = C_6H_5, Alk = CH_3 (**a**), CH_3CH_2 (**b**), Ar = 4-ClC_6H_4, Alk = CH_3CH_2 (**c**), Ar = 4-BrC_6H_4, Alk = CH_3 (**d**), CH_3CH_2 (**e**); R = C_6H_5, Ar = C_6H_5, Alk = CH_3 (**f**), CH_3CH_2 (**g**); R = 4-$CH_3C_6H_4$, Ar = C_6H_5, Alk = CH_3 (**h**), CH_3CH_2 (**i**); R = C_6H_{11}, Ar = 4-BrC_6H_4, Alk = CH_3 (**j**), CH_3CH_2 (**k**).

Organozinc compounds **IIa** and **IIb** reacted with electrophilic substrates **IIIa**–**IIIf** in diethyl ether–tetrahydrofuran (THF)–hexamethylphosphoramide (HMPA) in a regioselective fashion, giving rise to intermediates **IVa**–**IVk** via attack on C^3. Intermediates **IVa**–**IVk** underwent spontaneous cyclization to

the corresponding cyclopropanation products **Va**–**Vk**. The presence in molecules **Va**–**Vk** of an amide group activated due to replacement of hydrogen by the ZnBr group and of an ester moiety located at the same side of the cyclopropane ring plane creates favorable conditions for subsequent heterocyclization. In fact, attack by the amide group on the ester moiety results in formation of the corresponding alkyl 3-R-6-aryl-5-cyano-2,4-dioxo-3-azabicyclo[3.1.0]hexane-1-carboxamides **VIa**–**VIk** as final products.

The structure of compounds **VIa**–**VIk** was proved by the analytical data and ^{1}H NMR and IR spectra. The IR spectra of **VIa**–**VIk** characteristically contained absorption bands belonging to the ester carbonyl (1720–1725 cm^{-1}), lactam carbonyl (1700–1705, 1780–1800 cm^{-1}), and cyano groups (2240–2245 cm^{-1}). In the ^{1}H NMR spectra of these compounds we observed signals in the region δ 3.14–4.31 ppm due to the ArCH proton and those corresponding to protons of the ester methyl or ethyl radical at δ 3.63–3.74 (CH_3O) or 1.03–1.09 (CH_3CH_2O) and 4.08–4.14 ppm (CH_3CH_2O). As follows from the ^{1}H NMR spectra, compounds **VIa**–**VIk** are formed as a single stereoisomer. Taking into account the structure of initial compounds **IIIa**–**IIIf**, in which the bulky aryl and N-substituted carbamoyl groups are oriented trans with respect to each other, we presumed that the same arrangement of these substituents is typical of final products **VIa**–**VIk**.

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured from solutions in $CDCl_3$ (compounds **VIb**–**VIg**, **VIk)**, DMSO-d_6 (**VIj**), or DMSO-d_6–$CDCl_3$ (**VIh**) on a Tesla BS-567A spectrometer (100 MHz); the spectra of **VIa** and **VIi** were obtained from solutions in $CDCl_3$ on a Mercury-Plus-300 instrument (300 MHz); hexamethyldisiloxane was used as internal reference.

Alkyl 6-aryl-3-benzyl-5-cyano-2,4-dioxo-3-azabicyclo[3.1.0]hexane-1-carboxylates VIa–**VIe** *(general procedure).* Dimethyl or diethyl 2,2-dibromomalonate, 0.024 mol, was added to a mixture of 2 g of zinc (prepared as fine turnings), 7 ml of ethyl ether, and 10 ml of tetrahydrofuran. The mixture was heated to initiate a 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 the corresponding N-substituted 3-aryl-2-cyanoprop-2-enamide and 1.5 ml of HMPA, and the mixture was heated for 30–40 min under reflux. The mixture was cooled, treated with 5% acetic acid, and extracted with benzene. The solvent was distilled off from the extract, and the residue was recrystallized from methanol.

Methyl 3-benzyl-5-cyano-2,4-dioxo-6-phenyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (VIa). Yield 66%, mp 163–164°C. IR spectrum, ν, cm^{-1}: 1705, 1720, 1780, 2240. ^{1}H NMR spectrum, δ, ppm: 3.25 s (1H, CH), 3.67 s (3H, CH_3), 4.58 s (2H, CH_2Ph), 7.25–7.34 m (10H, $2C_6H_5$). Found, %: C 69.88; H 4.40; N 7.69. $C_{21}H_{16}N_2O_4$. Calculated, %: C 69.99; H 4.48; N 7.77.

Ethyl 3-benzyl-5-cyano-2,4-dioxo-6-phenyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (VIb). Yield 61%, mp 144–145°C. IR spectrum, ν, cm^{-1}: 1705, 1725, 1785, 2245. ^{1}H NMR spectrum, δ, ppm: 1.06 t (3H, CH_3CH$_2$), 3.27 s (1H, CH), 4.11 q (2H, CH_3·CH_2), 4.58 s (2H, CH_2Ph), 7.20–7.40 m (10H, $2C_6H_5$). Found, %: C 70.46; H 4.76; N 7.41. $C_{22}H_{18}$·N_2O_4. Calculated, %: C 70.58; H 4.85; N 7.48.

Ethyl 3-benzyl-6-(4-chlorophenyl)-5-cyano-2,4-dioxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (VIc). Yield 67%. mp 142–143°C. IR spectrum, ν, cm^{-1}: 1705, 1720, 1790, 2245. ^{1}H NMR spectrum, δ, ppm: 1.09 t (3H, CH_3CH$_2$), 3.23 s (1H, CH), 4.09 q (2H, CH_3CH_2), 4.56 s (2H, CH_2Ph), 7.10–7.30 m (9H, 4-ClC_6H_4, C_6H_5). Found, %: C 64.51; H 4.12; N 6.78. $C_{22}H_{17}ClN_2O_4$. Calculated, %: C 64.63; H 4.19; N 6.85.

Methyl 3-benzyl-6-(4-bromophenyl)-5-cyano-2,4-dioxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (VId). Yield 63%, mp 149–150°C. IR spectrum, ν, cm^{-1}: 1705, 1720, 1785, 2240. ^{1}H NMR spectrum, δ, ppm: 3.16 s (1H, CH), 3.63 s (3H, CH_3), 4.50 s (2H, CH_2Ph), 7.00–7.42 m (9H, C_6H_5, 4-BrC_6H_4). Found, %: C 57.31; H 3.34; N 6.30. $C_{21}H_{15}BrN_2O_4$. Calculated, %: C 57.42; H 3.44; N 6.38.

Ethyl 3-benzyl-6-(4-bromophenyl)-5-cyano-2,4-dioxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (VIe). Yield 69%, mp 143–144°C. IR spectrum, ν, cm^{-1}: 1705, 1720, 1780, 2240. ^{1}H NMR spectrum, δ, ppm: 1.07 t (3H, CH_3CH$_2$), 3.14 s (1H, CH), 4.08 q (2H, CH_3CH_2), 4.53 s (2H, CH_2Ph), 7.01–7.42 m (9H, C_6H_5, 4-BrC_6H_4). Found, %: C 58.21; H 3.72; N 6.11. $C_{22}H_{17}BrN_2O_4$. Calculated, %: C 58.29; H 3.78; N 6.18.

Alkyl 3,6-diaryl- and 6-aryl-3-cyclohexyl-5-cyano-2,4-dioxo-3-azabicyclo[3.1.0]hexane-1-carboxylates VIe–**VIi** were synthesized as described above for compounds **VIa**–**VIe**. The product crystallized from the reaction mixture on cooling to room

temperature and was filtered off and recrystallized from ethyl acetate.

Methyl 5-cyano-2,4-dioxo-3,6-diphenyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (VIf). Yield 67%, mp 234–235°C. IR spectrum, ν, cm^{-1}: 1705, 1725, 1800, 2240. ^1H NMR spectrum, δ, ppm: 3.64 s (1H, CH), 3.74 s (3H, $COOCH_3$), 7.10–7.50 m (10H, $2C_6H_5$). Found, %: C 69.28; H 4.01; N 8.02. $C_{20}H_{14}N_2O_4$. Calculated, %: C 69.36; H 4.07; N 8.09.

Ethyl 5-cyano-2,4-dioxo-3,6-diphenyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (VIg). Yield 64%, mp 181–182°C. IR spectrum, ν, cm^{-1}: 1700, 1725, 1795, 2240. ^1H NMR spectrum, δ, ppm: 1.09 t (3H, CH_3CH_2), 3.63 s (1H, CH), 4.14 q (2H, CH_3CH_2O), 7.10–7.50 m (10H, $2C_6H_5$). Found, %: C 69.89; H 4.41; N 7.70. $C_{21}H_{16}N_2O_4$. Calculated, %: C 69.99; H 4.48; N 7.77.

Methyl 5-cyano-3-(4-methylphenyl)-2,4-dioxo-6-phenyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (VIh). Yield 71%, mp 224–225°C. IR spectrum, ν, cm^{-1}: 1705, 1725, 1800, 2240. ^1H NMR spectrum, δ, ppm: 2.31 s (3H, CH_3), 3.66 s (3H, $COOCH_3$), 4.31 s (1H, CH), 7.05–7.30 m (9H, C_6H_5, $4\text{-}CH_3C_6H_4$). Found, %: C 69.90; H 4.42; N 7.71. $C_{21}H_{16}N_2O_4$. Calculated, %: C 69.99; H 4.48; N 7.77.

Ethyl 5-cyano-3-(4-methylphenyl)-2,4-dioxo-6-phenyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (VIi). Yield 68%, mp 199–201°C. IR spectrum, ν, cm^{-1}: 1700, 1725, 1795, 2240. ^1H NMR spectrum, δ, ppm: 1.03 t (3H, CH_3CH_2), 2.30 s (3H, CH_3), 3.63 s (1H, CH), 4.13 q (2H, CH_3CH_2O), 7.05–7.35 m (9H, C_6H_5, $4\text{-}CH_3C_6H_4$). Found, %: C 70.50; H 4.79; N 7.39. $C_{22}H_{18}N_2O_4$. Calculated, %: C 70.58; H 4.85; N 7.48.

Methyl 6-(4-bromophenyl)-5-cyano-3-cyclohexyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (VIj). Yield 73%, mp 250–252°C. IR spectrum, ν, cm^{-1}: 1705, 1725, 1780, 2245. ^1H NMR spectrum, δ, ppm: 1.05–2.20 m (10H, C_6H_{11}), 3.63 s (3H, CH_3), 3.65 m (1H, C_6H_{11}), 4.14 s (1H, CH), 7.15 d (2H, $4\text{-}BrC_6H_4$), 7.54 d (2H, $4\text{-}BrC_6H_4$). Found, %: C 55.62; H 4.35; N 6.43. $C_{20}H_{19}BrN_2O_4$. Calculated, %: C 55.70; H 4.44; N 6.50.

Ethyl 6-(4-bromophenyl)-5-cyano-3-cyclohexyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (VIk). Yield 78%, mp 221–222°C. IR spectrum, ν, cm^{-1}: 1705, 1720, 1780, 2240. ^1H NMR spectrum, δ, ppm: 1.08 t (3H, CH_3), 1.10–2.19 m (10H, C_6H_{11}), 3.15 s (1H, CH), 3.79 m (1H, C_6H_{11}), 4.10 q (2H, CH_2), 7.11 d (2H, $4\text{-}BrC_6H_4$), 7.35 d (2H, $4\text{-}BrC_6H_4$). Found, %: C 56.56; H 4.69; N 6.22. $C_{21}H_{21}BrN_2O_4$. Calculated, %: C 56.64; H 4.75; N 6.29.

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