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Reaction of Organozinc Reagents Prepared from Bromomalonic Acid Esters and Zinc with 3-Aryl-2-cyanopropenoic Acid Primary Amides

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Abstract—Organozinc compounds prepared from bromomalonic acid esters and zinc react with 3-aryl-2-cyanopropenoic acid primary amides giving a single diastereomer of the corresponding 1-R'-4-aryl-2,6-dioxo-5-cyanopiperidine-3-carboxylic acid esters, or 3-R'-6-aryl-2,4-dioxo-5- cyano-3-azabicyclo[3.1.0]hexene-1-carboxylic acid esters.

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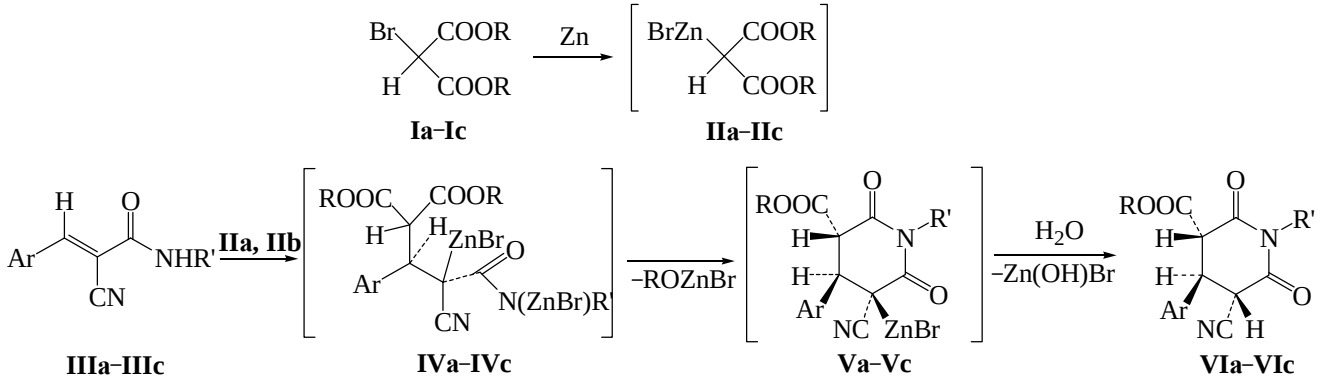
Reformatsky reagent prepared from methyl α-bromoisobutyrate and zink with 3-aryl-2-cyanopropenoic acid amides gave rise to 1-R-4-aryl-5,5-dimethyl-2,6-dioxopiperidine-3-carbonitriles [1]. The target of the present study was investigation of the reaction of organozinc reagents **IIa–IIc** obtained from bromomalonic acid esters **Ia–Ic** and zinc with primary amides of 3-aryl-2-cyanopropenoic acid **IIIa–IIIc**. The experiments proved the reaction to follow Scheme 1.

In a medium ethyl ether–tetrahydrofuran–hexamethylphosphoramide, 5:5:1, organozinc compounds **IIa–IIc** obtained from bromo derivatives **Ia–Ic** regiospecifically reacted with electrophilic substrates **IIIa–IIIc** with attack directed on an electron-deficient C^3 atom resulting in intermediate compounds **IVa–IVc**. Further cyclization of the latter led to the formation of intermediates **Va–Vc** whose hydrolysis provided 1-R'-4-aryl-2,6-dioxo-5-cyanopiperidine-3-carboxylic acid esters **VIa–VIc**.

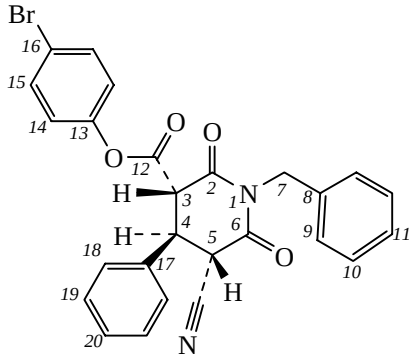
Scheme 1.



I, II, R = CH_3 (**a**), CH_3CH_2 (**b**), 4-BrC_6H_4 (**c**); **III**, R' = CH_2Ph, Ar = C_6H_5 (**a**), 4-ClC_6H_4 (**b**), 4-BrC_6H_4 (**c**); **IV–VI**, R' = CH_2Ph, R = CH_3, Ar = 4-BrC_6H_4 (**a**); R = CH_3CH_2, Ar = 4-ClC_6H_4 (**b**), R = 4-BrC_6H_4, Ar = C_6H_5 (**c**).

The composition and structure of compounds **VIa–VIc** were proved by elemental analysis, IR and ^{1}H NMR spectroscopy. The IR spectra contained the characteristic absorption bands of nitrile group (2250 cm^{-1}) and of carbonyls from ester (1730 cm^{-1}) and lactam (1670 cm^{-1}) groups. In the ^{1}H NMR spectrum of 4-bromophenyl 1-benzyl-2,6-dioxo-4-phenyl-5-cyanopiperidine-3-carboxylate (**VIc**) the following characteristic signals were observed, δ, ppm (DMSO-d_6, 300 MHz): 4.43 t, 4.78 d, 5.21 d (3H, C^{4}H, C^{3}H, C^{5}H) evidencing that the compound, as well as compounds **VIa** and **VIb**, formed as a single diastereomer. The spin-spin coupling constant of methine protons $J \approx 12.8$ Hz.

We elucidated the structural features of compounds obtained investigating 4-bromophenyl 1-benzyl-2,6-dioxo-4-phenyl-5-cyanopiperidine-3-carboxylate (**VIc**) by a combination of the methods of one-dimensional (^{1}H,^{13}C) and two-dimensional (2D ^{1}H-^{13}C HSQC, 2D ^{1}H–^{13}C HMBC) NMR spectroscopy (see EXPERIMENTAL).



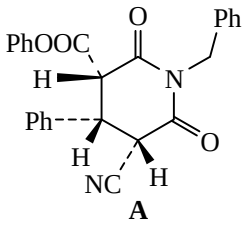
The protons of the piperidine ring H^3, H^4, and H^5 form a strongly coupled three-spin *ABC* system, for the difference in their chemical shifts is significantly less than their coupling constants. The analysis of the spectrum of the *ABC* system was carried out with the use of simulation and iteration procedures included into the program Mestre C [http://www.mestrec.com]. The best coincidence of the experimental and theoretic spectra was achieved at the following spectral parameters: δ_A 4.076, δ_B 4.047, δ_C 3.959 ppm, and J_{AB} –0.4, J_{AC} 12.7, J_{BC} 13.0 Hz.

The *C* proton with two large vicinal coupling constants corresponds to H^4 proton; however the theoretical calculation does not allow to assign *A* and *B* to definite nuclei. The signals were assigned to protons H^5 and H^3 based on the data of spectrum 2D ^{1}H ^{13}C HSQC. Atom C^5 (δ 43.22 ppm) shifted upfield with respect to atom C^3 (δ 55.68 ppm) due to the effect of a nitrile group was involved in a correlation pair with a proton at δ 4.05 ppm; thus the *B* signal of the *ABC* system corresponded to H^5 proton.

According to the data of heteronuclear experiment HMBC based on long-range coupling among the three signals from carbonyl groups carbons (C^2, C^6, C^{12}) only the signal with the chemical shift δ 164.42 ppm had no cross-peaks with H^7 protons suggesting that it belonged to atom C^{12}. We failed to assign unambiguously the signals of two other carbonyl carbons (C^2, C^6).

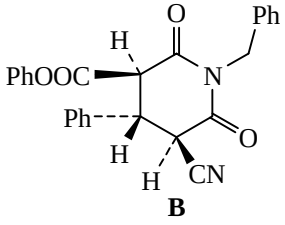
Judging from the values of vicinal coupling constants $^3J_{3,4}$ and $^3J_{4,5}$ the corresponding protons are located in the axial positions in the six-membered ring, therefore the substituents at C^3, C^4, and C^5 are present in the equatorial positions.

In order to obtain additional data on the structure of compounds synthesized we carried out a calculation of the geometry of phenyl 1-benzyl-2,6-dioxo-4-phenyl-5-cyanopiperidine-3-carboxylate by a semiempirical method SCF MO LCAO in the MNDO-PM3 approximation [2].



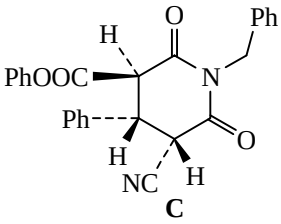
A

3*S*(*R*),4*S*(*R*),5*S*(*R*)
ΔH_f –21.85 kcal/mol
$\theta_{HC^3C^4H}$ 59.41°
$\theta_{HC^4C^5H}$ –50.75°
$^3J_{3,4}$ 4.08 Hz
$^3J_{4,5}$ 5.37 Hz



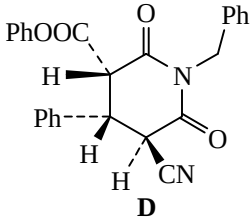
B

3*S*(*R*),4*R*(*S*),5*S*(*R*)
ΔH_f –29.21 kcal/mol
$\theta_{HC^3C^4H}$ 169.93°
$\theta_{HC^4C^5H}$ –178.37°
$^3J_{3,4}$ 12.68 Hz
$^3J_{4,5}$ 12.99 Hz



C

3*R*(*S*),4*S*(*R*),5*S*(*R*)
ΔH_f –30.65 kcal/mol
$\theta_{HC^3C^4H}$ 165.18°
$\theta_{HC^4C^5H}$ –60.61°
$^3J_{3,4}$ 12.31 Hz
$^3J_{4,5}$ 3.92 Hz



D

3*S*(*R*),4*R*(*S*),5*S*(*R*)
ΔH_f –29.21 kcal/mol
$\theta_{HC^3C^4H}$ 169.93°
$\theta_{HC^4C^5H}$ –178.37°
$^3J_{3,4}$ 12.68 Hz
$^3J_{4,5}$ 12.99 Hz

Theoretically this compound can exist in the form of four diastereomers **A**–**D**.

We determined for diastereomers **A**–**D** the enthalpies of formation ΔH_f and dihedral angles HC^3C^4H and HC^4C^5H. The data obtained made it possible to calculate the vicinal coupling constants $J_{3,4}$ and $J_{4,5}$ by Karplus equation with Buthner-By parameters [3], which in particular for diastereomer **B** turned out to be equal to 12.68 and 12.98 Hz respectively. Virtually complete coincidence of the theoretically calculated constants (12.68, 12.98 Hz) with experimental ones (12.7, 13.0 Hz) indicates that phenyl 1-benzyl-2,6-dioxo-4-phenyl-5-cyanopiperidine-3-carboxylate and also compounds **VIa** and **VIb** forms as diastereomer **B**. These data are fully consistent with the results of one-dimensional and two-dimensional NMR spectroscopy.

During the study we found one more direction of the reaction under investigation. Apparently due to the high α-CH-acidity of the esters of bromomalonic acid organozinc compounds **IIa** and **IIb** reacted with initial esters **Ia** and **Ib** forming reagents **VIIIa** and **VIIIb**, and the reaction in this case took the route presented in Scheme 2.

In a medium ethyl ether–tetrahydrofuran–hexamethylphosphoramide, 5:7:1, organozinc compounds **VIIIa** and **VIIIb** reacted regiospecifically with electrophilic substrates **IIIb, IIId**, and **IIIe** giving rise to intermediate compounds **IXa–IXc**. Intermediates **IXa–IXc** under the reaction conditions spontaneously underwent cyclization into the corresponding cyclopropanation products **Xa–Xc**. A presence in the intermediate compounds **Xa–Xc** of an amide group activated due to the replacement of a hydrogen by ZnBr moiety, and of an ester group on the same side as the amide group with respect to plane of the cyclopropane structural fragment provided a possibility for additional heterocyclization to occur. Actually, as the experiments demonstrated, the amide group attacked the ester one leading to the formation of 3-substituted alkyl 6-aryl-2,4-dioxo-5-cyano-3-azabicyclo[3.1.0]hexane-1-carboxylates **XIa–XIc**.

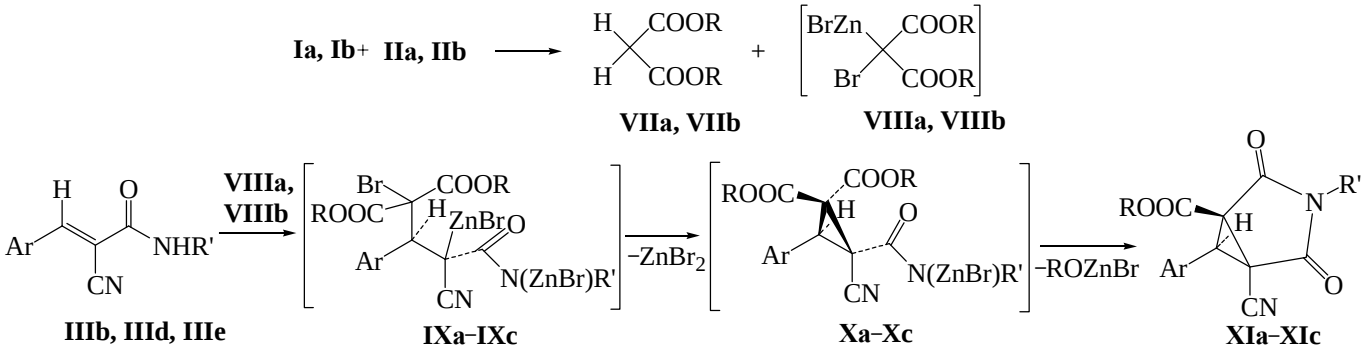
The composition and structure of compounds **XIa–XIc** were proved by elemental analysis, IR and ^{1}H NMR spectroscopy. The IR spectra contained the characteristic absorption bands of nitrile group (2260 cm^{-1}) and of carbonyls from ester (1720 cm^{-1}) and lactam (1700 cm^{-1}) groups. In the ^{1}H NMR spectra appear characteristic signals in the region 3.20–3.66 ppm belonging to the methine proton CH, proton signals from methyl and ethyl substituent of one ester group at δ, ppm: 3.57 (3H, CH_3O), 1.05 t (3H, $C\underline{H}_3CH_2O$), and 4.05 q (2H, $CH_3C\underline{H}_2O$).

Since in the initial compounds **IIIa–IIIe** the most bulky groups Ar and CONHR' are in the *trans*-position, it is presumable that the same position of the mentioned substituents is conserved also in the final reaction products **VIa–VIc** and **XIa–XIc**.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Specord 75IR from mulls of individual compounds in mineral oil. ^{1}H NMR spectra of compounds **VIa, VIb**, and **XIa–XIc**, in $CDCl_3$ solution were registered on a spectrometer Tesla BS-567A (100 MHz), internal reference HMDS, spectrum of compound **VIc** in DMSO-d_6, on a spectrometer Mercury-Plus 300 (300 MHz),

Scheme 2.



VII, VIII, R = CH_3 (**a**), CH_3CH_2 (**b**), **III**, R' = CH_2Ph, Ar = 4-ClC_6H_4 (**b**), R' = C_6H_5, Ar = C_6H_5 (**d**); Ar = 4-BrC_6H_4, R' = C_6H_{11} (**d**); **IX–XI**, R = CH_3, Ar = 4-BrC_6H_4, R' = C_6H_{11} (**a**); R = CH_3CH_2, Ar = C_6H_5, R' = C_6H_5 (**a**), Ar = 4-ClC_6H_4, R' = CH_2Ph (**b**).

internal reference HMDS. 1D- and 2D-NMR spectra from solution of compound **VIc** in $CDCl_3$ were registered on Bruker DRX-400 instrument [400 (^{1}H) and 100 MHz (^{13}C)], internal reference TMS .

1-R'-4-Aryl-2,6-dioxo-5-cyanopiperidine-3-carboxylic acid esters VIa–VIc. To 0.01 mol of 3-aryl-2-cyanopropenoic acid amide and 1.5 g of zinc was added as solvent a mixture of ethyl ether–THF–HMPA, 5:5:1. The mixture was heated till complete dissolution of the substrate, the heating was removed, and 0.023 mol of bromomalonic acid ester was added dropwise. The reaction mixture started spontaneously to boil. On completing the addition of the reagent the reaction mixture was heated at reflux for 30–40 min, then it was cooled, hydrolyzed with 10% solution of acetic acid, the reaction product was extracted into ether, the extract was dried with Na_2SO_4, the solvent was distilled off, and the residue was thrice recrystallized from methanol.

Methyl 1-benzyl-4-(4-bromophenyl)-2,6-dioxo-5-cyanopiperidine-3-carboxylate (VIa). Yield 2.3 g (52%), mp 138–140°C. IR spectrum, ν, cm^{-1}: 1670, 1730, 2250. ^{1}H NMR spectrum, δ, ppm: 3.57 s (3H, $COOCH_3$), 3.65–4.05 m (3H, H^3, H^4, H^5), 4.92 s (2H, $C\underline{H}_2C_6H_5$), 6.65–7.50 m (9H, C_6H_5, C_6H_4). Found, %: C 57.01; H 3.73; N 7.33. $C_{21}H_{17}BrN_2O_4$. Calculated, %: C 57.14; H 3.85; N 6.35.

Ethyl 1-benzyl-2,6-dioxo-4-(4-chlorophenyl)-5-cyanopiperidine-3-carboxylate (VIb). Yield 2.2 g (54%), mp 129–130°C. IR spectrum, ν, cm^{-1}: 1670, 1730, 2250. ^{1}H NMR spectrum, δ, ppm: 1.05 t (3H, $C\underline{H}_3CH_2O$, *J* 7.5 Hz), 3.60–3.90 m (3H, H^3, H^4, H^5), 4.05 q (2H, $CH_3C\underline{H}_2O$, *J* 7.5 Hz), 4.94 s (2H, $C\underline{H}_2C_6H_5$), 7.05–7.40 m (9H, C_6H_5, 4-ClC_6H_4). Found, %: C 64.19; H 4.54; N 6.75. $C_{22}H_{19}ClN_2O_4$. Calculated, %: C 64.31; H 4.63; N 6.82.

4-Bromophenyl 1-benzyl-2,6-dioxo-4-phenyl-5-cyanopiperidine-3-carboxylate (VIc). Yield 2.3 g (45%), mp 161–163°C. IR spectrum, ν, cm^{-1}: 1680, 1750, 2270. ^{1}H NMR spectrum (300 Hz, DMSO-d_6), δ, ppm: 4.43 t (1H, H^4, *J* 12.8 Hz), 4.78 d (1H, H^3, *J* 12.8 Hz), 4.94 d (1H, H^{7b}, *J* 17.5 Hz), 4.99 d (1H, H^{7a}, *J* 17.5 Hz), 5.21 d (1H, H^5, *J* 12.8 Hz), 6.64 d (2H, H^{14}, *J* 8.7 Hz), 7.25–7.60 m (14H, C_6H_5, $CH_2C_6\underline{H}_5$, 4-BrC_6H_4). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 3.95 d.d (1H, H^4, *J* 13.0, 12.7 Hz), 4.08 d (1H, H^3, *J* 12.7 Hz), 4.05 d (1H, H^5, *J* 13.0 Hz), 5.04 d (1H, H^{7b}, *J* 13.7 Hz), 5.08 d (1H, H^{7a}, *J* 13.7 Hz), 6.61 d (2H, H^{14}, *J* 8.9 Hz), 7.36–7.30 m (5H, C^4-C_6H_5), 7.40 d (2H, H^{15}, *J* 8.9 Hz), 7.48–7.42 m (5H, $CH_2C_6H_5$). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 42.12 (C^4), 43.22 (C^5), 44.85 (C^7), 55.68 (C^3), 113.29 (CN), 119.79 (C^{16}), 122.85 (C^{14}), 127.33 (C^{18}), 128.36 (C^{20}), 128.76 (C^{19}), 129.48 (C^9), 129.73 (C^{11}), 129.80 (C^{10}), 132.61 (C^{15}), 134.24 (C^{17}), 135.39 (C^8), 148.93 (C^{13}), 163.24 (C$^{6/2}$), 164.42 (C^{12}), 166.16 (C$^{2/6}$). Found, %: C 61.89; H 3.67; N 5.48. $C_{26}H_{19}BrN_2O_4$. Calculated, %: C 62.02; H 3.78; N 5.57.

6-Aryl-3-R'-2,4-dioxo-5-cyano-3-azabicyclo-[3.1.0]hexane-1-carboxylic acid esters XIa–XIc. To 2 g of fine zinc turnings in 5 ml of ether and 7 ml of THF was added 0.03 mol of bromomalonic acid ester. The mixture was heated till the reaction started, and then it continued spontaneously. On completion of the reaction the mixture was heated for 5 min. cooled, and decanted from zinc into a flask charged with 0.01 mol of 3-aryl-2-cyanopropenoic acid N-substituted amide and 1 ml of HMPA, and then boiled for 30–40 min. On cooling the reaction mixture was hydrolyzed with 5% acetic acid, the reaction product was extracted into ether, the solvent was distilled off, and the residue was recrystallized from methanol.

Methyl 6-(4-bromophenyl)-2,4-dioxo-5-cyano-3-cyclohexyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (XIa). Yield 2.7 g (63%), mp 250–251°C. IR spectrum, ν, cm^{-1}: 1700 1720, 1790, 2260. ^{1}H 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-BrC_6H_4, *J* 8.7 Hz), 7.54 d (2H, 4-BrC_6H_4, *J* 8.7 Hz). 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 3,6-diphenyl-2,4-dioxo-5-cyano-3-azabicyclo[3.1.0]hexane-1-carboxylate (XIb). Yield 2.4 g (60%), mp 190–191°C. IR spectrum, ν, cm^{-1}: 1665, 1715, 1800, 2270. ^{1}H NMR spectrum, δ, ppm: 1.09 t (3H, $C\underline{H}_3CH_2$, *J* 7.5 Hz), 3.63 s (1H, CH), 4.14 q (2H, $CH_3C\underline{H}_2$, *J* 7.5 Hz), 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.

Ethyl 3-benzyl-2,4-dioxo-6-(4-chlorophenyl)-5-cyano-3-azabicyclo[3.1.0]hexane-1-carboxylate (XIc). Yield 2.4 g (56%), mp 140–141°C. IR spectrum, ν, cm^{-1}: 1670, 1720, 1780, 2250. ^{1}H NMR spectrum, δ, ppm: 1.11 t (3H, $C\underline{H}_3CH_2$, *J* 7.5 Hz), 3.20 s (1H, CH), 4.13 q (3H, $CH_3C\underline{H}_2$, *J* 7.5 Hz), 4.58 s (2H, $C\underline{H}_2C_6H_5$) 7.15–7.40 m (10H, $2C_6H_5$). Found, %: C 64.50; H 4.07;

N 6.78. $C_{22}H_{17}ClN_2O_4$. Calculated, %: C 64.63; H 4.16; N 6.85.

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