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Reactions of Methyl 1-Bromocyclohexylcarboxylate with Zinc and Benzyl- or Cyclohexylamides of 3-Aryl-2-cyanopropenoic Acids

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Abstract—Methyl 1-bromocyclohexylcarboxylate reacts with zinc and benzyl- or cyclohexylamides of 3-aryl-2-cyanopropenoic acids to give methyl 1-(1-aryl-3-benzylamino)- or methyl 1-(1-aryl-3-cyclohexylamino)-3-oxo-2-cyanopropyl)cyclohexylcarboxylates whose structure was determined by XRD analysis.

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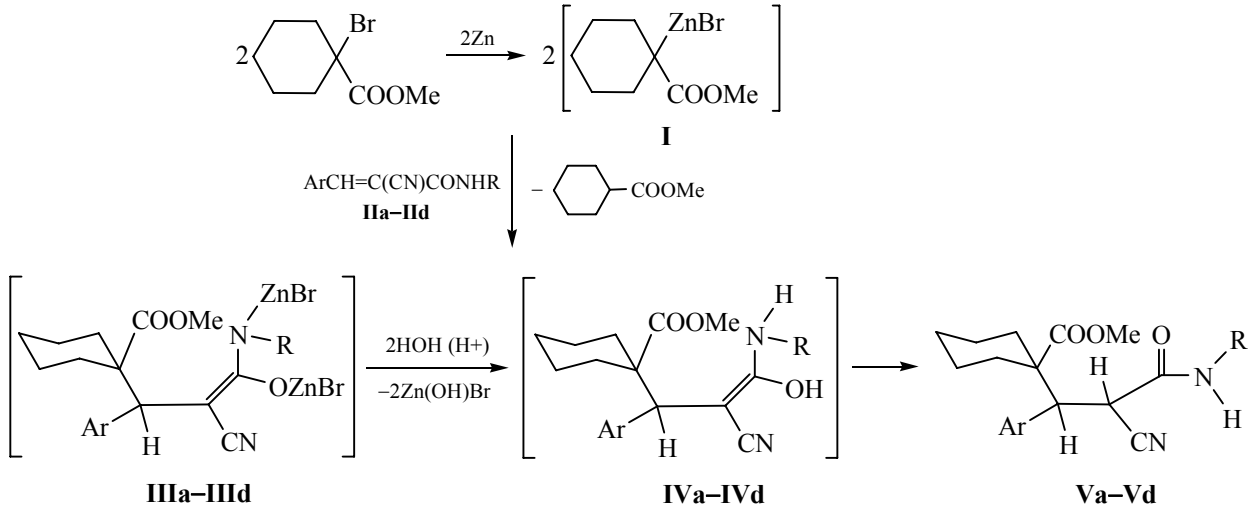
It was found previously that Reformatsky reagents add to the double bond of amides of 3-aryl-2-cyanopropenoic acids followed by cyclization of intermediates to form substituted piperidine-2,6-diones [1–4]. We have studied the reaction of the Reformatsky reagent **I** obtained from methyl 1-bromocyclohexylcarboxylate and zinc, with benzyl- and cyclohexylamides of 3-aryl-2-cyanopropenoic acids. The Reformatsky reagent **I** in boiling benzene reacts with unsaturated amide at the 1,4-positions to form intermediates **IIIa**–**IIId**. After decomposing the reaction mixture methyl 1-(1-aryl-3-benzylamino-3-oxo-2-cyanopropyl)cyclohexylcarboxylates **Va**, **Vb** or methyl 1-(1-aryl-3-oxo-2-cyano-3-cyclohexylpropyl) cyclohexylcarboxylates **Vc**, **Vd** were isolated.

In this case there is no cyclization of adducts into piperidine-2,6-diones through the attack of the nitrogen atom on the ester carbonyl group. Probably, it is caused by the bulky cyclohexyl substituent bonded with an ester group and the substituents at the nitrogen atom in the intermediates **IIIa**–**IIId**.



IIIa–IIId **IVa–IVd** **Va–Vd**

II–V, R = $C_6H_5CH_2$, Ar = 4-BrC_6H_4 (**a**), 3-BrC_6H_4 (**b**); R = C_6H_{11}, Ar = Ph (**c**), 3-BrC_6H_4 (**d**).

Some bonds lengths, bond and torsion angles in compound **Va**

Bond, angle	Å, deg	Bond, angle	Å, deg
$Br^1–C^{14}$	1.919(5)	$Br^{1A}–C^{14A}$	1.903(4)
$N^1–C^5$	1.319(5)	$N^{1A}–C^{5A}$	1.323(5)
$N^1–C^{25}$	1.458(5)	$N^{1A}–C^{25A}$	1.467(5)
$O^1–C^1$	1.211(6)	$O^{1A}–C^{1A}$	1.203(5)
$C^1–O^2$	1.310(6)	$C^{1A}–O^{2A}$	1.324(6)
$N^2–C^{17}$	1.140(5)	$N^{2A}–C^{17A}$	1.157(5)
$O^3–C^5$	1.223(4)	$O^{3A}–C^{5A}$	1.216(4)
$C^4–C^5$	1.545(5)	$C^{4A}–O^{5A}$	1.531(5)
$N^1–C^{25}–C^{18}$	113.2(4)	$N^{1A}–C^{25A}–C^{18A}$	111.9(4)
$C^{17}–C^4–C^5$	105.0(3)	$C^{17A}–C^{4A}–C^{5A}$	104.9(3)
$C^{17}–C^4–C^3$	110.2(3)	$C^{17A}–C^{4A}–C^{3A}$	110.0(3)
$C^5–C^4–C^3$	114.7(3)	$C^{5A}–C^{4A}–C^{3A}$	114.3(3)
$N^2–C^{17}–C^4$	179.4(4)	$N^{2A}–C^{17A}–C^{4A}$	178.6(4)
$C^{17}C^4C^5N^1$	–96.8(4)	$C^{17A}C^{4A}C^{5A}N^{1A}$	98.0(4)
$C^1C^2C^3C^{11}$	62.0(5)	$C^{1A}C^{2A}C^{3A}C^{11A}$	–59.2(4)
$C^{10}C^2C^3C^{11}$	–173.5(4)	$C^{10A}C^{2A}C^{3A}C^{11A}$	59.9(4)
$C^6C^2C^3C^{11}$	–55.1(5)	$C^{6A}C^{2A}C^{3A}C^{11A}$	179.6(4)
$C^1C^2C^3C^4$	–65.5(5)	$C^{1A}C^{2A}C^{3A}C^{4A}$	68.6(4)
$C^2C^3C^4C^{17}$	168.9(3)	$C^{2A}C^{3A}C^{4A}C^{17A}$	–167.7(3)

The composition and structure of compounds **Va**–**Vd** were confirmed by the elemental analysis data and IR and ^{1}H NMR spectroscopy. The IR spectra of compounds **Va**–**Vd** contain an absorption band in the regions of 1660–1665 and 1730–1740 cm^{-1}, respectively, belonging to the carbonyls of ester and amide groups. The ^{1}H NMR spectra ($CDCl_3$) indicate that compounds **Va**–**Vd** were isolated as a racemic mixture of one the two possible diastereomers. The most characteristic signals are the doublets of doublets of non-equivalent methylene protons of benzyl substituent in the amide fragment of compounds **Va**, **Vb** at 4.11–4.17 and 4.45–4.46 ppm and the protons doublets of oxopropyl moiety in the ranges of 3.48–3.55 and 3.92–4.04 ppm with spin-spin coupling constants of 3.0–3.3 Hz. To establish the structure of the compounds obtained we investigated compound **Va** by XRD analysis.

According to the XRD analysis data, two crystallographically independent molecules crystallize in a chiral space group *P*1 of triclinic system. Numbers of the atoms of the second molecule were marked with an additional index "A." The molecules have similar bond lengths and angles, but different absolute configuration (see Table). In particular, the atoms C^3 and C^4 have *S*-configuration, and the atoms C^{4A} and C^{3A}, *R*-configuration (Figs. 1 and 2). Despite the fact that the composition of the unit cell is racemic, the molecular organization is not centrosymmetrical. This is due to the formation of intermolecular hydrogen bonds N–H···O, by which the molecules are arranged in a chain along *b* axis. In this case the non-centrosymmetrical alternation of the molecules of different configuration is preferable, where the bulky groups at the atoms C^2 and C^{2A} and also the polar CN groups are spatially separated and aryl substituents are stacked as compact as possible (Fig. 3).

Thus, the crystallization of compound **Va** is a rare case of the formation of chiral triclinic crystal system formed by two enantiomers.

EXPERIMENTAL

The IR spectra were obtained on a spectrophotometer Specord-75IR from the samples in mineral oil. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a

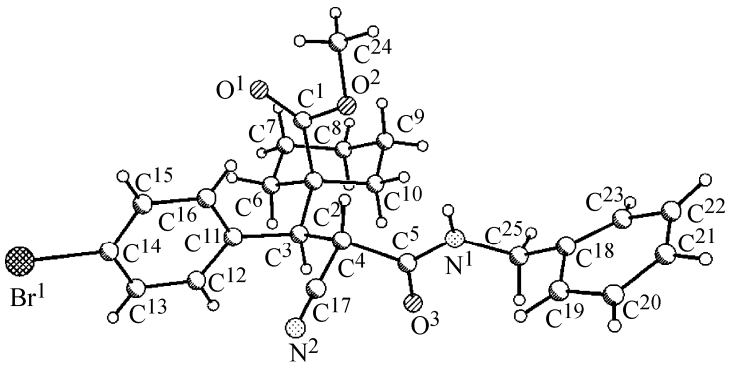


Fig. 1. Ball-and-stick model of compound **Va** (first molecule) according to XRD data.

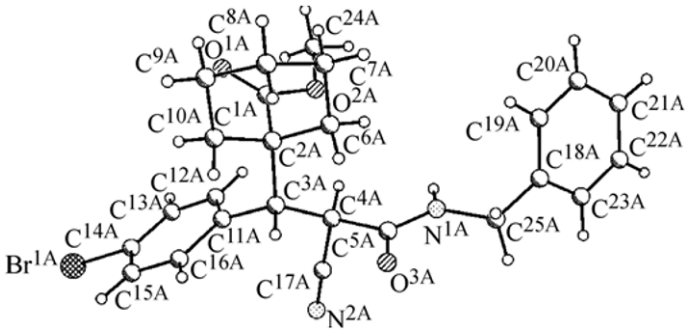


Fig. 2. Ball-and-stick model of compound **Va** (second molecule) according to XRD data.

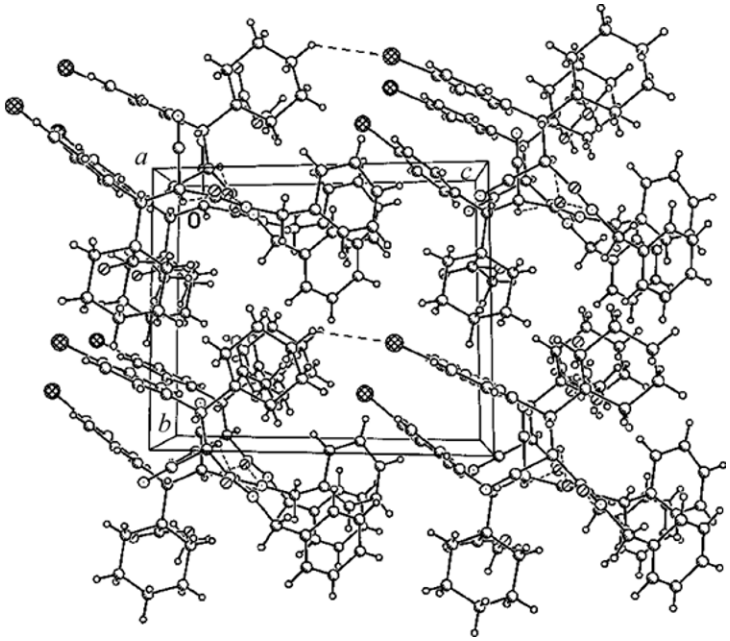


Fig. 3. Fragment of molecular packing of compound **Va**.

Mercury Plus-300 spectrometer (300 MHz) with respect to internal TMS.

The XRD diffraction analysis of compound **Va** was performed on an automatic four-circle diffractometer Xcalibur 3 equipped with CCD-detectors at 295(2) K [λ(MoK_α) 0.71073 Å). Collection and processing of data obtained was carried out by the standard procedure [5], the extinction correction was introduced by multiscanning method [6]. The crystals are triclinic, space group *P*1, *a* 9.3552(10), *b* 10.6498(10), *c* 12.8109(11) Å; α 86.843(7), β 75.502(8), γ 79.417(8)°, μ 1.719 mm^{-1} . In the range of 2.87 <θ <28.28° 11339 reflections were collected, 6760 were independent (R_{int} 0.0207), including 3047 with $I > 2\sigma(I)$. The completeness for θ < 26.00° is 97.1%. The solution and refinement of the structure was carried out using the software package SHELX [7]. The structure was refined by full-matrix least-square method with respect to F^2 in anisotropic approximation for all non-hydrogen atoms. The hydrogen atoms were placed into the geometrically calculated positions and refined isotropically with dependent thermal parameters by a *rider* model. The final refinement results: R_1 0.0418, wR_2 0.0840 [for reflections with $I > 2\sigma(I)$], R_1 0.1035, wR_2 0.0893 (for all reflections) at *Q*-factor *GOOF* of 1.004. The absolute structure parameter is –0.002(7). The peaks of maximal and minimal residual electron density are 0.501 and –0.505 *e* $Å^{-3}$. The results of XRD diffraction experiments are deposited in the Cambridge Structural Database (CCDC 900795).

General procedure for the preparation of compounds Va–Vd. A mixture of 3 g of fine zinc turnings, a catalytic amount of mercuric chloride, 20 ml of anhydrous ethyl acetate, 20 ml of anhydrous benzene, 1 ml of HMPA, 10 mmol benzylamide (or cyclohexylamide) of 3-aryl-2-cyanopropenoic acid and

25 mmol of methyl 1-bromocyclohexylcarboxylate was refluxed for 4 h, cooled, decanted from an excess of zinc and treated with 5% of acetic acid. The organic layer was separated, and the aqueous layer was extracted twice with ethyl acetate. After drying the extract over anhydrous sodium sulfate, the solvent was distilled off, and the target compound was recrystallized from ethyl acetate.

Methyl 1-[3-(benzylamino)-1-(4-bromophenyl)-3-oxopropyl-2-cyano]cyclohexylcarboxylate (Va). Yield 1.04 g (43%), mp. 176–177°C. IR spectrum, ν, cm^{-1}: 3270 (NH), 1730 (C=O, ester), 1660 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 1.04–2.37 m [10H, $(CH_2)_5$], 3.54 d (1H, C^3H, *J* 3.0 Hz), 3.78 s (3H, MeO), 4.01 d (1H, C^2H, *J* 3.0 Hz), 4.11 d. d (1H, C<u>H</u>Ph, *J* 16.6, 4.8 Hz), 4.46 d. d (1H, C<u>H</u>Ph, *J* 16.6, 6.9 Hz), 6.33 br. s (1H, NH), 6.83 d (2H, *J* 7.5 Hz), 7.22–7.27 m (5H, Ph), 7.14 d (2H, *J* 8.7 Hz), 7.40 d (4H, 4-BrC_6H_4, *J* 8.7 Hz). Found, %: C 61.99; H 5.74; Br 16.68; N 5.88. $C_{25}H_{27}BrN_2O_3$. Calculated, %: C 62.12; H 5.63; Br 16.53; N 5.80.

Methyl 1-[3-(benzylamino)-1-(3-bromophenyl)-3-oxopropyl-2-cyano]cyclohexylcarboxylate (Vb). Yield 0.92 g (38%), mp 158–159°C. IR spectrum, ν, cm^{-1}: 3270 (NH), 1730 (C=O, ester), 1660 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 1.08–2.38 m [10H, $(CH_2)_5$], 3.55 d (1H, C^3H, *J* 3.3 Hz), 3.79 s (3H, MeO), 4.04 d (1H, C^2H, *J* 3.3 Hz), 4.17 d. d (1H, C<u>H</u>Ph, *J* 15.0, 4.8 Hz), 4.45 d. d (1H, C<u>H</u>Ph, *J* 15.0, 6.9 Hz), 6.34 br. s (1H, NH), 6.89 d (2H, *J* 7.2 Hz), 7.22–7.25 m (5H, Ph), 7.16 t (1H, *J* 8.1 Hz), 7.27 d (1H, *J* 8.1 Hz), 7.41 s, 7.45 d (4H, 3-BrC_6H_4, *J* 8.1 Hz). Found, %: C 62.23; H 5.66; Br 16.41; N 5.94. $C_{25}H_{27}BrN_2O_3$. Calculated, %: C 62.12; H 5.63; Br 16.53; N 5.80.

Methyl 1-[3-oxopropyl-1-phenyl-2-cyano-3-(cyclohexylamino)]cyclohexylcarboxylate (Vc). Yield 1.03 g (52%), mp 153–154°C. IR spectrum, ν, cm^{-1}: 3275 (NH), 1740 (C=O, ester), 1665 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 0.98–2.37 m [20H, $2(CH_2)_5$], 3.49 d (1H, C^3H, *J* 3.3 Hz), 3.53–3.63 m (1H, CHN), 3.77 s (3H, MeO), 3.92 d (1H, C^2H, *J* 3.3 Hz), 5.61 d (1H, NH, *J* 8.4 Hz), 7.28 s (5H, Ph). Found, %: C 72.84; H 8.06; N 6.98. $C_{24}H_{32}N_2O_3$. Calculated, %: C 72.70; H 8.13; N 7.06.

Methyl 1-[1-(3-bromophenyl)-3-oxopropyl-2-cyano-3-(cyclohexylamino)]cyclohexylcarboxylate (Vd). Yield 1.35 g (57%), mp 172–173°C. IR spectrum, ν, cm^{-1}: 3260 (NH), 1730 (C=O, ester), 1660 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 0.70–2.38 m [20H, $2(CH_2)_5$], 3.48 d (1H, C^3H, *J* 3.3 Hz), 3.54–3.66 m (1H, CHN), 3.79 s (3H, MeO), 3.93 d (1H, C^2H, *J* 3.3 Hz), 5.73 d (1H, NH, *J* 6.9 Hz), 7.19 t (1H, *J* 7.8 Hz), 7.29 d (1H, *J* 7.8 Hz), 7.37 s, 7.43 d (4H, 3-BrC_6H_4, *J* 7.8 Hz). Found, %: C 60.49; H 6.70; Br 16.58; N 5.93. $C_{24}H_{31}BrN_2O_3$. Calculated, %: C 60.63; H 6.57; Br 16.81; N 5.89.

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REFERENCES

1. Shchepin, V.V. and Fotin, D.V., *Zh. Org. Khim.*, 2005, vol. 41, no. 7, p. 1034.
2. Shchepin, V.V., Silaychev, P.S., Stepanyan, Yu.G., Vakhrin, M.I., Yozhikova, M.A., and Kodess, M.I., *Zh. Org. Khim.*, 2006. T. 42. MY. 11. S. 1639.
3. Shchepin, V.V., Stepanyan, Yu.G., Silaychev, P.S., Russkikh, N.Yu., Shurov, S.N., and Rakitin, A.R., *Zh. Obshch. Khim.*, 2006, vol. 76, no. 11, p. 1888.
4. Kirillov, N.F., Nikiforova, E.A., Shurov S.N., Slepukhin, P.A., and Vakhrin, M.I., *Zh. Obshch. Khim.*, 2012, vol. 82, no. 7, p. 1124.
5. *CrysAlis CCD*, Version 1.171.29.9, Oxford Diffraction Ltd., 2006.
6. *CrysAlis RED*, Version 1.171.29.9, Oxford Diffraction Ltd., 2006.
7. Sheldrick, G.M., *Acta Cryst*., 2008, no. 64, p. 112.