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SYNTHESIS OF SUBSTITUTED COUMARINS AND THEIR CARBORANE DERIVATIVES AS POTENCIAL ANTICANCER DRUGS

Abstract. In this paper, we present the reactions of the conjugated addition of C-metal derivative of boron-rich compound – lithium-*o*-carborane to the coumarins: 3-acetylbromcoumarin, 3-carbethoxycoumarin and products of its substitution with aromatic nitrogen-containing compounds. Getting the latter was performed here for the first time; the dependence of the reaction direction on the basicity of the amine was shown – the low basic amine (indole) is attached to the 4-position of 3-carbethoxycoumarin, while the more basic amines (aniline and 2-amino-6-methylpyridin) led to obtainment of the classical carboxamides. These initial compounds were introduced into the reaction of conjugated addition with isopropyl lithium-*o*-carborane. There are row of the products of this interaction: 3-indolo-3-carbonyl-4-(isopropyl-*o*-carborane)-3,4-dihydrocoumarin, 3-(2-amino-6-methylpyridino)-3-carbonyl-4-(isopropyl-*o*-carboran)-3,4-dihydrocoumarin and 3-anilino-3-carbonyl-4-(isopropyl-*o*-carboran)-3,4-dihydrocoumarin. Reaction of 3-acetylbromcoumarin with lithium-*o*-carborane in equivalent amount gives 3-carbonyl-3-isopropyl-*o*-carboranoyl coumarin; whereas two amount of isopropyl lithium-*o*-carborane leads to the 3-carbonyl-3-isopropyl-*o*-carboranoyl-4-(isopropyl-*o*-carborane)-3,4-dihydrocoumarin.

Key words: 3-carbethoxycoumarin, 3-acetylcoumarin, *o*-carboran, boron neutron capture therapy of cancer, organic synthesis.

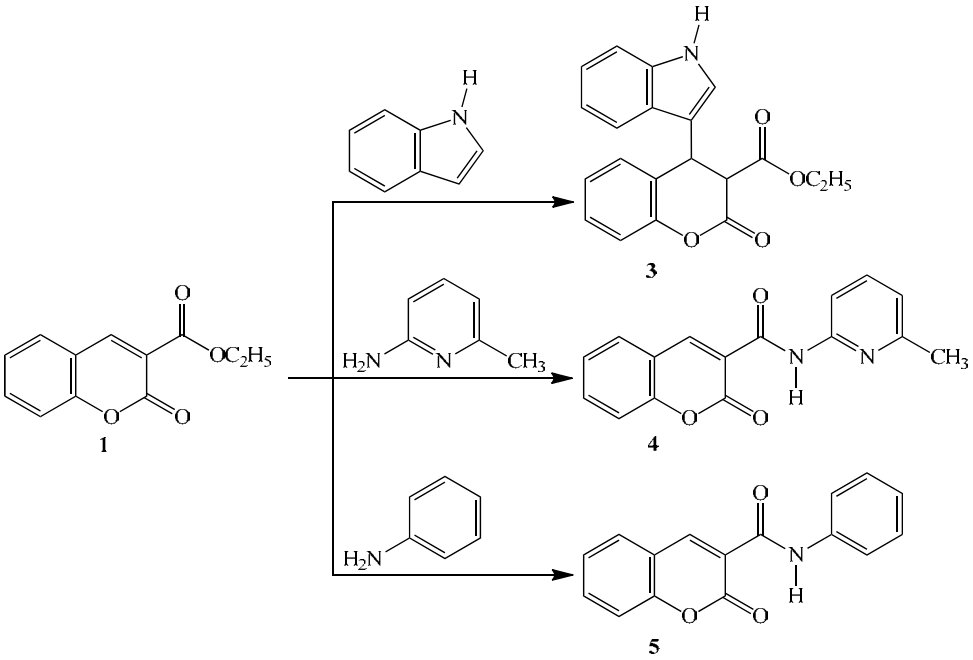
Introduction. Coumarins and their derivatives have a wide range of biological activity [1]. They are able to bind heavy metal ions, quench free radical processes, and others. Moreover coumarin derivatives have wide range of the therapeutic properties, such as antispasmodic, coronary expanding, choleretic, anti-inflammatory, antiallergic. The versatility of these hybrid compounds makes them potential candidates for drugs to treat multifactorial diseases: cancer, Alzheimer's disease, metabolic syndromes, AIDS, malaria and cardiovascular diseases [1–5]. Another potential application of such hybrid compounds is boron neutron capture therapy of cancer (BNCT). At the present moment method of BNCT is under considerable attention the scientists around the world. This treatment mode of cancer include: administering of specific boron compounds, which are absorbed only by the cancer cells and are accumulated inside the cancer cells; at irradiating by neutrons boron compounds and neutrons collide and cause atomic fission, producing α-Ray radiation which destroys the cancer cells from inside. However, in order to successfully realize the unique capabilities of BNCT in clinical practice, it is necessary to solve complex chemical, biological, medical and physico-technical problems. At first potential drugs for BNCT should be soluble in water, should

have: low toxicity, biological and chemical stability, maximum amount of boron atoms, and be selective to tumor cells [6–10]. Carboranes have special interests for scientists involved in research of drugs for BNCT. A large amount of boron (10 atoms) per molecule makes them promising for use in the development of drugs for BNCT. For icosahedron carboranes, the methods for their appending into different organic/biochemical compounds are well known. Huge amount of published paper are devoted to research *o*-carborane derivatives [8–12]. At present, the clinical practice of BNCT relies on two preparations: 4-dihydroxy borophenyl alanine [13], and mercapto-closo-dodecaborate sodium [14], and many other boron delivery agents are under evaluation [13–15]. However, 4-dihydroxy borophenyl alanine does not have a sufficient amount of boron, and the mercapto-closo-dodecaborate sodium does not exhibit selectivity for cancer cells. Therefore, the search for drugs for BNCT is a priority task. To date, carboranyl-containing functionally substituted derivatives of coumarins have been studied by a group of scientists under the leadership of Prof. A.V. Kazantsev [16–19]. Such structures include heterocyclic fragments of a different nature, giving these compounds unique chemical and pharmacological properties. In the continuation of these studies, the article describes the reactions of first modified 3-substituted coumarines with isopropyl lithium-*o*-carborane.

RESULTS AND DISCUSSIONS

The most accessible and having several reaction centers for the addition of carborane derivatives, 3-carbethoxycoumarin **1** and 3-acetylcoumarin **2** were chosen as initial compounds. Compounds **1** and **2** were synthesized by the Knovenagel reaction: by the condensation of salicylic aldehyde and acetoacetic ester in the presence of piperidine as a catalyst [20] and by the condensation of salicylic aldehyde and malonic ester in the presence of the piperidine/acetic acid/ethanol as catalytic system [4]. To establish the various features of the C-metal attachment of carborane, various derivatives of these compounds were obtained. The reaction of 3-carbethoxycoumarin with indole, aniline and 2-amino-6-methylpyridine was carried out.

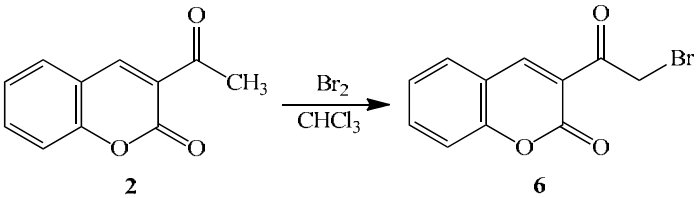
The reaction of 3-carbethoxycoumarin **1** with indole gives 3,4-dihydrocoumarin **3** because of ^{1}H NMR spectra of **3** contains proton signals of CH_2CH_3 group at δ 1.38 ppm and δ 4.38 ppm, proton signal of 4th position of starting coumarin **1** at δ 8.56 ppm [21] is absent in the ^{1}H NMR spectrum of compound **3**. Proton signals at 3- and 4-carbon atoms of 3,4-dihydrocoumarin **3** exist at δ 4.18 and 5.01 ppm and have spin-spin interaction with the constant J = 7.2 Hz. The total intensity of the signals of aromatic protons $C_{sp2}H$ in the region of δ 6.81–7.65 ppm is 9H. Aniline and 2-amino-6-methylpyridine react by the ether component of 3-carbethoxycoumarin (**1**).



Their ^{1}H NMR spectra does not contain proton signals of C_2H_5 group, while signals of proton at 4th position of coumarins **4** and **5** are still exist in ^{1}H NMR spectra at δ 9.00 ppm; proton signals of NH group of these compounds are at δ 11.30 and 10.90 ppm, respectively. The total intensities of the signals of aromatic protons $C_{sp2}H$ of the compounds **4** and **5** in the regions of δ 6.94–9.00 ppm and δ 7.14–9.00 ppm amount 8H and 10H, respectively.

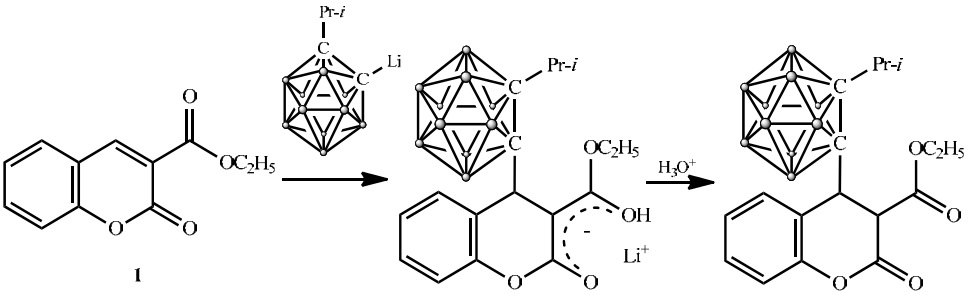
Differences of the reaction directions may be explained by the fact of various basicity of indole and aniline and 2-amino-6-methylpyridine. The lone electron pair of indole nitrogen atom is delocalized throughout the aromatic ring and not available for protonation that explains the absence of basic properties of indole. However, the electrophilic substitution can take place to the 4th position of the carbon atom .

Bromine-derivative of 3-acetylcoumarin **6** was synthesized according to the work [20]:



The synthesis of carboranyl containing coumarin derivatives was based on conjugated addition reactions, which were first described in [17]. Developing studies of conjugate addition reactions in the series of C-metal derivatives of

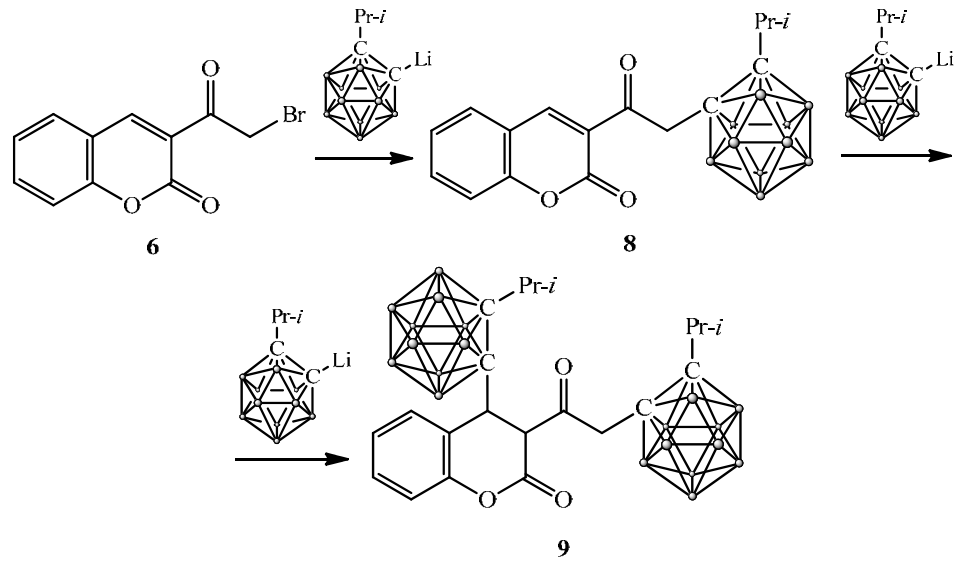
carboranes, we studied in detail the interaction of isopropyl lithium-*o*-carborane with 3-ethoxycarbonylcoumarin (**1**), 3-acetobromcoumarin (**2**), 3-indolo-3-carbonyl-3,4-dihydrocoumarin (**3**), 3-anilino-3-carbonyl-3,4-dihydrocoumarin (**4**) and 3-(2-amino-6-methylpyridino)-3-carbonyl-3,4-dihydrocoumarin (**5**). As a result of the conducted research, it was established that lithium derivatives of isopropyl-*o*-carboran in ether-benzene medium and tetrahydrofuran react with 3-carbethoxycoumarin (**1**) only according to the 1,4-addition scheme:



1 **7**

Structure **7** is supported by the main absorption bands in the FTIR-spectra at ν, cm^{-1}: 2987 (C_{sp2}–H), 2906 (C_{sp3}–H), 1732, 1755 (C=O); stretching vibration bands of carborane core ν_{B-H} are at 2576, 2616 cm^{-1}. Proton signals of BH group were detected in ^{1}H NMR spectrum as a broad multiplet at δ 1.6–2.5 ppm.

The interaction of lithium derivative of isopropyl-*o*-carboran with 3-acetylbromocoumarine (**6**) proceeds in two directions:

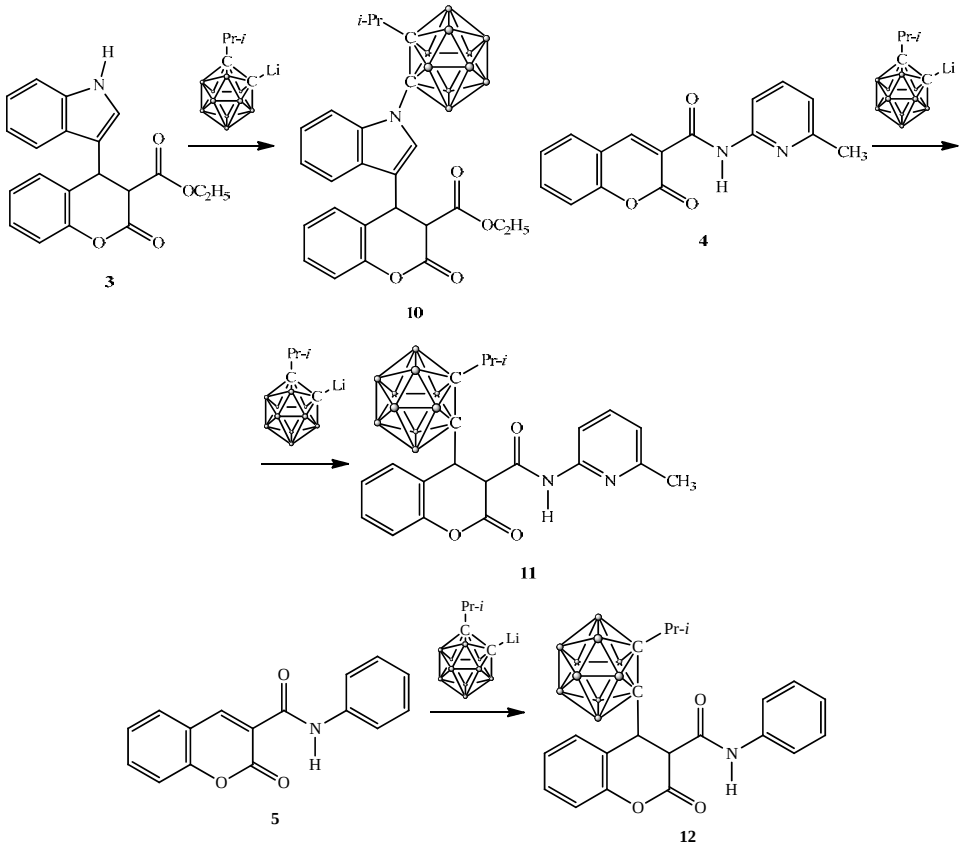


6 **8** **9**

The yield and structure of the final product essentially depends on the ratio and the order of mixing the reagents. When the ratio of reagents is 1:1, isopropyl-*o*-carboranyl lithium reacts via more reactive C–Br bond of coumarin **8**, FTIR

spectrum of this sample **8** does not contain characteristic bands ν_{C-Br} at 666 cm^{-1}; at the same time, in ^1H NMR spectrum proton of 4^{th} position of coumarine **8** at 9.00 pmm (1H, s) was detected. With an increase in the mole fraction of isopropyl-*o*-carboranyl lithium to two, carborane is also added to the 4th position of the lactone ring **9**.

To search for new potential biologically active substances, we also studied the interaction of an equimolar amount of lithium carborane derivatives with various substituted coumarins **3**–**5**. Products of substitution on protons in the groups NH were obtained: 4-indolo-3-carbonyl-4-(isopropyl-*o*-carborane)-3,4-dihydrocoumarin (**10**), 3-(2-amino-6-methylpyridino)-3-carbonyl-4-(isopropyl-*o*-carboran)-3,4-dihydrocoumarin (**11**) and 3-anilino-3-carbonyl-4-(isopropyl-*o*-carborane)-3,4-dihydrocoumarin (**12**) with high yields (65, 84 and 87%, respectively). IR-Spectra and spectra ^1H NMR of the product **10** does not contain band of stretching bond ν_{N-H} of and proton signal of NH group.



In the IR spectrum of the product **10** following characteristic bands are present, ν, cm^{-1}: 2568 (B–H), 1739, 1672 (C=O), 1231(C–N); ^1H NMR spectrum contains proton signals, ppm (*J*, Hz): 1.01 (3H, t, *J* = 7.1, CH_2–$C\underline{H_3}$), 1.33–1.42

(6H, dd, J = 6.8, (C<u>H</u>$_3$)$_2$CH), 2.57–2.63 (1H, m, C<u>H</u>(CH$_3$)$_2$), 3.48 (1H, d, J = 7.2), 5.3 (1H, d, J = 7.2), 4.01–4.15 (2H, m, C<u>H</u>$_2$–CH$_3$), 6.92–7.91 (9H), m, C_{sp2}H), 1.6–2.3 (10H, m, BH).

Both structures **11** and **12** were supported by IR and ^{1}H NMR spectroscopy. IR-spectra of **11** and **12** contain bands, ν, cm^{-1}: 2565, 2615 and 2566, 2615 (B–H), 1670 and 1712 and 1648, 1705 (C=O). ^{1}H NMR spectra of the structures **11** and **12** have the following characteristic proton signals, δ, ppm (J, Hz): 1.19–1.29 and 1.27–1.40 [6H, dd, J = 6.8, (C<u>H</u>$_3$)$_2$CH], 2.5 and 3.52 [1H, m, (C<u>H</u>(CH$_3$)$_2$], 4.71 and 3.64 (1H, s, NH), 1.4–2.2 and 1.5–2.3 (10H, m, BH), 3.45 (1H, d, J = 7.2, C_{sp3}H) and 5.2, 5.3 (1H, d, J = 7.2, C_{sp3}H). Synthesized carboranyl-containing coumarins will be further tested as potential drugs for boron-neutron capture therapy of cancer using the ^{10}B (n, α, γ) ^{7}Li (B-NRT) reaction.

EXPERIMENT

FTIR spectra were recorded on Cary 600 Series FTIR spectrometer manufactured by Agilent Technologies (USA) using a single reflection attachment on a Gladiatr diamond manufactured by PIKE (USA). The NMR spectra were recorded on "JNM-ECA Series FT NMR" (JEOL) model ECA 500, at 500 MHz. Melting point were obtained on "Buchi Melting Point M560" device. The elemental analysis for carbon, hydrogen and boron were done by the express-gravimetric method (for boron, in the presence of lead (II) oxide). Nitrogen was determined by Dumas – Pregl – Kite method. The reactions were monitored by TLC on Sorbfil plates sorbent-loaded silica gel with 8–12 μm grain size. Solvents (EtOH, *i*-PrOH, DCE (1,2-dichloroethane), hexane, ether, benzene, THF, petroleum ether and ethyl acetate used in the reactions and at recrystallization, were prepared according to accepted methods [22].

*4-Indolo-3-carbonyl-3,4-dihydrocoumarin (**3**).* 1.17 g (0.01 mol) of indole was added to the alcoholic solution of 2.18 g (0.01 mol) of 3-carbethoxycoumarin with stirring. The mixture was boiled for 10 h and controlled by TLC. The solution was cooled, the precipitate **3** was filtered and washed with cold EtOH, the residue was recrystallized from EtOH. Yield of the product **3** amounted 2.67 g (80%), mp 241–243 °C (EtOH), R_f 0.35 (7/3, EtOAc/hexane as eluent). Found, %: C 71.47; H 5.01; N 4.11. $C_{20}H_{17}NO_4$. Calculated, %: C 71.63; H 5.11; N 4.18. FTIR spectrum, ν, см$^{-1}$: 3357 (N–H), 2982, 3060 (C_{sp2}–H), 1715, 1768 (C=O). ^{1}H NMR spectrum ($CDCl_3$), ppm (J, Hz): 8.16 (1H, s, NH), 7.02–7.65 (8H, m, C_{sp2}H), 6.81 (1H, d, J =3.6, C(2)$_{sp2}$H indole), 5.01 (1H, d, J = 7.2, C_{sp3}H), 4.38 (2H, q, J = 7.2, CH$_3$C<u>H</u>$_2$), 4.18 (1H, d, J = 7.2, C_{sp3}H), 1.38 (3H, t, J = 7.2, C<u>H</u>$_3$CH$_2$).

*3-(2-Amino-6-methylpyridino)-3-carbonyl-3,4-dihydrocoumarin (**4**).* To the alcoholic solution of 2.18 g (0.01 mol) of 3-carbethoxycoumarin, 1.08 g (0.01 mol) of 2-amino-6-methylpyridine was added with stirring. The mixture was boiled for 10 h. The reaction was monitored by TLC. The solution was cooled, the precipitate was filtered. Then it was washed with cold EtOH. After the drying and

recrystallization of the residue from *i*-PrOH yield of the product **12** was 2.05 g (63%), mp 226–228 °C, R_f 0.82 (1/2, EtOAc/hexane as eluent). Found, %: C 68.41; H 4.22; N 9.83. $C_{16}H_{12}N_2O_3$. Calculated, %: C 68.56; H 4.32; N 9.99. FTIR spectrum, ν, см$^{-1}$: 3237 (N–H), 3052 (C_{sp2}–H), 1667, 1717 (C=O), 1231 (C–N). ^{1}H NMR spectrum ($CDCl_3$), ppm (*J*, Hz): 11.30 (1H, s, NH), 9.00 [1H, s, $C(4)_{sp2}H$], 8.13 (1H, d, *J* = 7.4 Hz, $C_{sp2}H$), 7.59–7.74 (3H, m, $C_{sp2}H$), 7.38–7.46 (2H, m, $C_{sp2}H$), 6.94 (1H, d, *J* = 7.4 Hz), 2.50 (3H, s, CH_3).

*3-Anilino-3-carbonyl-3,4-dihydrocoumarin (**5**).* To the alcoholic solution of 2.18 g (0.01 mol) of 3-carbethoxycoumarin, 0.93 g (0.01 mol) of aniline was added with stirring. The reaction mixture with TLC control was stirred for 10 h. After distilling off the solvent on a vacuum evaporator and drying of the residue **5** on an air for 10 h and its recrystallization from DCE-hexane yield of the product **5** was 1.77 g (57%), mp 252–253 °C, R_f 0.75 (1/2, EtOAc/hexane as eluent). Found: C 72.27; H 4.02; N 5.16. $C_{16}H_{11}NO_3$. Calculated, %: C 72.45; H 4.18; N 5.28. FTIR spectrum, ν, см$^{-1}$: 3238 (N–H), 3047 (C_{sp2}–H), 1698, 1719 (C=O), 1248 (C–N). ^{1}H NMR spectrum ($CDCl_3$), ppm: 10.90 (1H, s, NH), 9.00 [1H, s, $C(4)_{sp2}H$], 7.68–7.76 (4H, m, $C_{sp2}H$), 7.36–7.47 (4H, m, $C_{sp2}H$), 7.14–7.19 (1H, m, $C_{sp2}H$).

*3-Ethoxycarbonyl-4-(isopropyl-o-carborane)-3,4-dihydrocoumarin (**7**).* 2.18 g (0.01 mol) of 3-carbethoxycoumarin was added to a benzene solution of 0.01 mol of 1-isopropyl-2-lithium-*o*-carboran obtained from 1.86 g (0.01 mol) of isopropyl-*o*-carboran and 0.011 mol (1.5N) 7.33 ml of a BuLi solution. The mixture was stirred for 1 h under an inert atmosphere, treated with dilute HCl and then extracted with benzene. After distilling off the solvent on a vacuum evaporator and recrystallizing the residue in EtOH yield of the product **7** was 3.27 g (80%), mp 189–191 °C, R_f 0.67 (1/2, EtOAc/hexane as eluent). Found, %: C 50.29; H 6.72; B 26.56. $C_{17}H_{28}B_{10}O_4$. Calculated, %: C 50.48; H 6.98; B 26.73. FTIR spectrum, ν, см$^{-1}$: 2987 (C_{sp2}–H), 2906 (C_{sp3}–H), 1732, 1755 (C=O), 2576, 2616 (B–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.13–7.25 (3H, m, $C_{sp2}H$), 7.38–7.42 (1H, m, $C_{sp2}H$), 5.3 (1H, d, *J* = 7.2), 4.21 (1H, d, *J* = 7.2), 1.34–1.4 [6H, dd, *J* = 6.8, $CH(C\underline{H}_3)_2$], 2.59–2.63 [1H, m, $(C\underline{H}(CH_3)_2$], 4.04 (2H, m, $C\underline{H}_2CH_3$), 1.6–2.5 (10H, m, BH), 1.0 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$).

*3-Carbonyl-3-isopropyl-o-carboranoyl coumarin (**8**).* 1.34 g (0.005 mol) of 3-bromo-3-carbonyl-3,4-dihydrocoumarin (**6**) was added to a solution of 0.005 mol of 1-isopropyl-2-lithium-*o*-carboran in 5 ml benzene. The mixture was stirred for 3 h under an inert atmosphere, treated with dilute HCl and extracted with benzene. After distilling off the solvent on a vacuum evaporator and recrystallizing in DCE-hexane, the residue yield of the product **8** was 1.41 g (62%), mp 182–185 °C (DCE-hexane), R_f 0.68 (1/2, EtOAc/hexane as eluent). Found, %: C, 51.40; H, 6.32; B, 28.88. $C_{16}H_{24}B_{10}O_3$. Calculated, %: C, 51.59; H, 6.49; B, 29.02. FTIR spectrum, ν, см$^{-1}$: 2980, 3028 (C_{sp2}–H), 2573 (B–H), 1606, 1720 (C=O). ^{1}H NMR spectrum ($CDCl_3$), ppm (*J*, Hz): 9.00 [1H, s, $C(4)_{sp2}H$], 7.25 (1H, m, $C_{sp2}H$), 7.52–7.53 (3H, m, $C_{sp2}H$); 0.89–0.95 (2H, m, CH_2), 1.37–1.45 (6H, dd, *J* = 6.8, $CH(C\underline{H}_3)_2$), and 2.5 (1H, m., $C\underline{H}(CH_3)_2$); 1.65–2.4 (10H, m, BH).

*3-Carbonyl-3-isopropyl-o-carboranoyl-4-(isopropyl-o-carborane)-3,4-dihydrocoumarin (**9**).* 1.34 g (0.005 mol) of 3-bromo-3-carbonyl-3,4-dihydrocoumarin (**8**) is added to solution of 0.01 mol of 1-isopropyl-2-lithium-*o*-carboran in 8 ml benzene. The mixture was stirred for 3 h under an inert atmosphere, after completion of the reaction (monitored by TLC), the mixture was treated with dilute HCl, and then extracted with benzene. After distilling off the solvent on a vacuum evaporator and recrystallizing in DCE-hexane. Yield of the product **9** amounted 1.66 g (51%), mp 191–195 °C (DCE-hexane), R_f 0.72 (1/2, EtOAc/hexane as eluent). Found, %: C 44.97; H 7.42; B 38.52. $C_{21}H_{42}B_{20}O_3$. Calculated, %: C 45.14; H 7.58; B 38.69. FTIR spectrum, ν, см$^{-1}$: 2958 (C_{sp2}–H), 2572, 2620 (B–H), 1608, 1720 (C=O). ^{1}H NMR spectrum ($CDCl_3$), ppm (*J*, Hz): 7.23 (1H, m, $C_{sp2}H$), 7.52–7.53 (3H, m, $C_{sp2}H$), 5.21 (1H, d, *J* = 7.2), 4.3 (1H, d, *J* = 7.2), 0.87–0.94 (2H, m, CH_2), 1.38–1.46 [12H, dd, *J* = 6.8, $2CH(C\underline{H}_3)_2$], and 2.5 (2H, m, $2C\underline{H}(CH_3)_2$); 1.65–2.4 ppm (20H, m, BH).

*3-Indolo-3-carbonyl-4-(isopropyl-o-carborane)-3,4-dihydrocoumarin (**10**).* 1.62 g (0.005 mol) of 3-indolo-3-carbonyl-3,4-dihydrocoumarin (**3**) was added at room temperature to the solution of 0.005 mol of 1-isopropyl-2-lithium-*o*-carboran in 5 ml benzene. The mixture was stirred for 3 h under argon atmosphere with TLC monitoring. After 5 h the reaction mixture was treated with dilute HCl, and extracted with benzene. After distilling off the solvent on a vacuum evaporator and recrystallizing in benzene-petroleum ether, the residue yield of the product **10** was 1.67 g (65%), mp 180–183 °C (benzene-petroleum ether), R_f 0.76 (2/3, EtOAc/hexane as eluent). Found, %: C 57.63; H 6.28; B 20.64. $C_{25}H_{33}B_{10}NO_4$. Calculated, %: C 57.78; H 6.40; B 20.80. FTIR spectrum, ν, см$^{-1}$: 2980 (C_{sp2}–H), 2568, 2615 (B–H), 1672, 1739 (C=O), 1231 (C–N). ^{1}H NMR spectrum ($CDCl_3$), ppm (*J*, Hz): 1.01 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$), 1.33–1.42 [6H, dd, *J* = 6.8 Hz, $CH(C\underline{H}_3)_2$], 2.57–2.63 [1H, m, $C\underline{H}(CH_3)_2$], 3.48 (1H, d, *J* = 7.2, $C_{sp3}H$), 5.3 (1H, d, *J* = 7.2, $C_{sp3}H$), 4.01–4.15 (2H, m, $C\underline{H}_2CH_3$), 6.92–7.91 (9H, m, $C_{sp2}H$), 1.6–2.3 (10H, m, BH).

*3-(2-Amino-6-methylpyridino)-3-carbonyl-4-(isopropyl-o-carboran)-3,4-dihydrocoumarin (**11**).* 0.33 g (0.001 mol) of 3-(2-amino-6-methylpyridino)-3-carbonyl-3,4-dihydrocoumarin (**4**) was added at room temperature to the solution of 0.001 mol 1-isopropyl-2-lithium-*o*-carboran in 5 ml benzene. The mixture was stirred for 3 h under argon atmosphere and then was treated with dilute HCl and extracted with benzene. After distilling off the solvent on a vacuum evaporator and recrystallizing in THF–hexane mixture, the residue yield of the product **11** was 0.44 g (84%), mp 159–162 °C, R_f 0.75 (1/5, EtOAc/hexane as eluent). Found: C 53.88; H 6.30; B 22.98. $C_{21}H_{30}B_{10}N_2O_3$. Calculated, %: C 54.06; H 6.48; B 23.17. FTIR spectrum, ν, см$^{-1}$: 3247 (N–H), 2976 (C_{sp2}–H), 2565, 2615 (B–H), 1670, 1712 (C=O). ^{1}H NMR spectrum ($CDCl_3$), ppm (*J*, Hz): 1.19–1.29 (6H, dd, *J* = 6.8, $CH(C\underline{H}_3)_2$], 2.5 [1H, m, $(C\underline{H}(CH_3)_2$], 4.71 (1H, s, NH), 7.16–7.21 (3H, m, $C_{sp2}H$), 7.34 (1H, m, $C_{sp2}H$), 6.65–6.77 (1H, m, $C_{sp2}H$), 6.93–7.00 (1H, m, $C_{sp2}H$), 7.76–7.77 (1H, m, $C_{sp2}H$), 3.45 (1H, d, *J* = 7.2, $C_{sp3}H$), 5.2 (1H, d, *J* = 7.2, $C_{sp3}H$), 1.4–2.2 (10H, m, BH), 1.75 (3H, s, CH_3).

3-anilino-3-carbonyl-4-(isopropyl-o-carboran)-3,4-dihydrocoumarin ***(12).*** 0.38 g (0.00125 mol) of 3-anilino-3-carbonyl-3,4-dihydrocoumarin (**5**) was added at room temperature to the solution of 0.00125 mol of 1-isopropyl-2-lithium-*o*-carboran in 5 ml benzene. The mixture was stirred for 3 h under argon atmosphere; and then it was treated with dilute HCl, and extracted with benzene. After distilling off the solvent on a vacuum evaporator and recrystallizing in DCE-hexane mixture, the residue yield of the product **12** was 0.54 g (87%), mp >400 °C (DCE-hexane), R_f 0.76 (1/5, EtOAc/hexane as eluent). Found, %: C 55.75; H 6.33; B 23.80. $C_{21}H_{29}B_{10}NO_3$. Calculated, %: C 55.86; H 6.47; B 23.94. FTIR spectrum, ν, $см^{-1}$: 3289 (N–H), 2982, 3047 (C_{sp2}–H), 2566, 2615 (B–H), 1648, 1705 (C=O). ^{1}H NMR spectrum ($CDCl_3$), ppm (*J*, Hz): 1.27–1.40 [6H, dd, *J* = 6.8, $(C\underline{H}_3)_2CH$], 3.52 [1H, m, $C\underline{H}(CH_3)_2$], 6.69–6.77 (1H, m, $C_{sp2}H$), 7.10–7.23 (3H, m, $C_{sp2}H$), 7.35–7.40 ppm (1H, m, $C_{sp2}H$), 7.68–7.75 (4H, m, $C_{sp2}H$); 3.45 (1H, d, *J* = 7.2, $C_{sp3}H$), 5.3 (1H, d, *J* = 7.2, $C_{sp3}H$), 3.64 (1H, s, NH) 1.5–2.3 (10H m, BH).

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Резюме

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ОРЫНБАСҚАН КУМАРИНДЕР МЕН ОЛАРДЫҢ КАРБОРАНДЫ ТУЫНДЫЛАРЫ СИНТЕЗІ ІСІККЕ ҚАРСЫ ПРЕПАРАТТАР РЕТІНДЕ ПРЕПАРАТАРДЫҢ ЖӘНЕ АУЫСТЫРЫЛҒАН КУМАРИНДЕРДІҢ СИНТЕЗІ

Берілген жұмыста 3-ацетилкумарин және 3-карбэтоксикумарин орынбасқан кумариндер қатарының С-металдық карборан туындыларымен қосарласқан қосылу реакцияларының зерттеу нәтижелері көрсетілген. 3-Карбэтоксикумариннің ароматы азоткұрамды қосылыстармен реакциялары зерттелді. Қолданылған амин негізділігіне реакция бағытының тәуелділігі көрсетілген: төменнегіздік амин 3-карбэтоксикумариннің 4-орынына қосылады, соған сәйкес жоғарынегізді аминдер классикалық карбоксиамидтердің алынуына алып келді. Алынған қосылыстармен изопропиллитий-о-карборанмен қосарласқан қосылу реакциясы жүргізілді, нәтижесінде 3-индоло-3-карбонил-4-(изопропил-*о*-карборанил)-3,4-дигидрокумариннің, 3-(2-амино-6-метилпиридино) – 3 – карбонил – 4 - (изопропил-*о*-карборанил)-3,4-дигидрокумариннің және 3-анилино-3-карбонил-4-(изопропил-*о*-карборанил)-3,4-дигидрокумариннің алынуына алып келді. Сондай-ақ, литийкарборан 3-ацетилбромкумарин беретін кезде 1:1 арақатынасында 3-карбонил хлорид-3-изопропил-*о*-карборанил кумарин өнімі, ал 1:2 қатынасы қосарланған қосылу карборан бойынша ацильді тобының өнімі және 4 ереже лактон сақиналар-3-карбонил-3-изопропил-*о*-карборанил-4-(изопропил-*о*-карборан)-3,4-дигидрокумарин реакцияның ерекшеліктері өтуіне көрсетілген.

Түйін сөздері: 3-карбэтоксикумарин, 3-ацетилкумарин, *о*-карборан, БНЗТ, органикалық синтез.

Резюме

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СИНТЕЗ ЗАМЕЩЕННЫХ КУМАРИНОВ
И ИХ КАРБОРАНОВЫХ ПРОИЗВОДНЫХ
КАК ПОТЕНЦИАЛЬНЫХ ПРОТИВОРАКОВЫХ ПРЕПАРАТОВ

В данной работе представлены результаты исследований реакций сопряженного присоединения С-металлических производных карборанов в ряду замещенных кумаринов – 3-карбэтоксикумарина и 3-ацетилкумарина. Изучены реакции 3-карбэтоксикумарина с ароматическими азотсодержащими соединениями. Показана зависимость направления реакции от основности взятого амина: низкоосновный амин присоединяется в 4-положении 3-карбэтоксикумарина, в то время как высокоосновные амины привели к получению классических карбоксамидов. Полученные соединения введены в реакцию сопряженного присоединения с изопропиллитий-*о*-кабораном, что приводило к образованию 3-индоло-3-карбонил-4-(изопропил-*о*-карборанил)-3,4-дигидрокумарина, 3-(2-амино-6-метилпиридино)-3-карбонил-4-(изопропил-*о*-карборанил) -3,4-дигидрокумарина и 3-анилино-3-карбонил-4- (изопропил-*о*-карборанил) -3,4-дигидрокумарина. Также показаны особенности протекания реакции литийкарборана с 3-ацетилбромкумарином, дающей при соотношении 1:1 продукт 3-карбонил-3-изопропил-*о*-карборанил кумарин, а при соотношении 1:2 продукт двойного присоединения карборана по ацильной группе и в 4 положение лактонного кольца - 3-карбонил-3-изопропил-*о*-карборанил-4- (изопропил-*о*-карборан) -3,4-дигидрокумарин.

Ключевые слова: 3-карбэтоксикумарин, 3-ацетилкумарин, *о*-карборан, БНЗТ, органический синтез.