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Synthesis of Azomethines Based on 4-Formylphenyl *m*-Carboranyl-*C*-methanoate

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Abstract—A preparative method for the synthesis of *m*-carborane azomethines via the condensation of *m*-carborane-*C*-4-formylphenyl methanoate with aliphatic, cycloaliphatic, and aromatic amines was developed.

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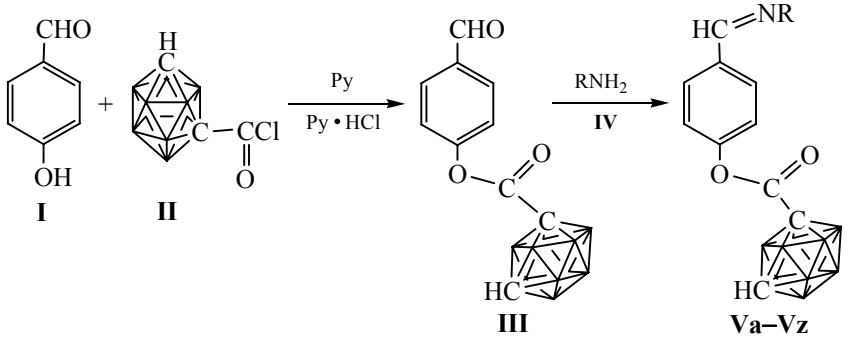
Previously a synthesis has been reported of *o*(*m*)-carborane-containing azomethines starting from *o*(*m*)-carboranyl-*C*-methylene-4-formyl benzoates [1]. The nitrogen-containing carborane derivatives are of interest as the agents in the boron neutron capture therapy of the neoplastic diseases, radionuclide diagnostics and therapy [2, 3].

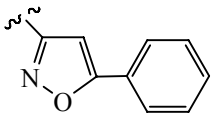
In this work we describe a method of the preparative synthesis of new *m*-carborane azomethines **V** via the condensation of 4-formylphenyl *m*-carboranyl-*C*-methanoate **III** with aliphatic, cycloaliphatic, and aromatic amines **IV**. The yield of compounds **V** was 85–89%. The starting 4-formylphenyl *m*-carboranyl-*C*-methanoate **III** was synthesized by the esterification of 4-formylmethanol **I** with *m*-carboranyl-*C*-carboxylic acid chloride **II** in the presence of pyridine in 91% yield.

The resulting carborane derivatives **III**, **Va**–**Vz** are crystalline or amorphous glassy substances, soluble in Et_2O, DMF, DMSO, and $CHCl_3$. The composition of compounds **III** and **V** was proved by the elemental analysis and molecular weight determination (see the table), the structure, by spectral methods.



I **II** **III** **Va–Vz**

V, R = *n*-$C_{18}H_{37}$ (**a**), CH(1-Ad)Me (**b**), *L*-CH(CHMe$_2$)CO_2Me (**c**), *L*-CH(CHCH$_2$Me$_2$)CO_2Me (**d**), *L*-CH(CHMeEt)CO_2Me (**e**), C_6H_5 (**f**), 4-MeC_6H_4 (**g**), 2-biphenyl (**h**), 4-biphenyl (**i**), 1-naphthyl (**j**), 2-naphthyl (**k**), 4-FC_6H_4 (**l**), 3-BrC_6H_4 (**m**), 4-BrC_6H_4 (**n**), 4-IC_6H_4 (**o**), 1-bromo-2-naphthyl (**p**), 2-hydroxyphenyl (**q**), 4-ethoxyphenyl (**r**), 4-phenoxyphenyl (**s**), 4-MeC(O)C_6H_4 (**t**), 4-EtC(O)C_6H_4 (**u**), C_6H_4-3-COOH (**v**), C_6H_4-4-COOH (**w**), C_6H_4-4-COOEt (**x**), C_6H_4-4-COOBu (**y**),



(**z**).

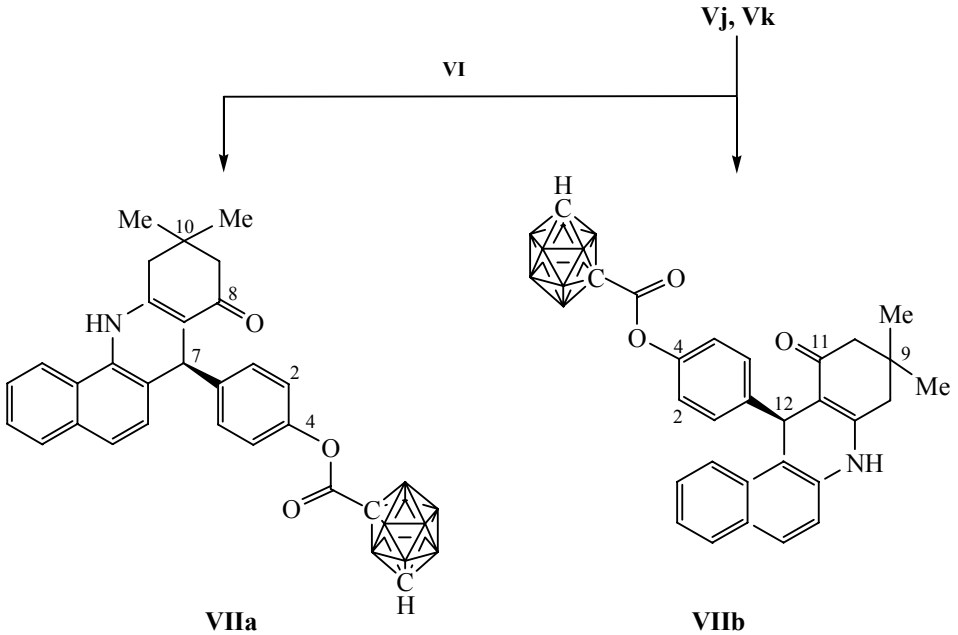
Yields, melting points, and elemental analysis data of compounds **III**, **V,** and **VII**

Comp. no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %				*M*	
			C	H	B	N		C	H	B	N	found	calculated
III	91	103–104	41.25	5.64	36.62	–	$C_{10}H_{16}B_{10}O_3$	41.08	5.52	36.98	–	284.6	292.3
IVa	85	44–45	61.98	9.89	19.45	2.32	$C_{28}H_{53}B_{10}NO_2$	61.84	9.82	19.88	2.58	527.4	543.8
IVb	87	60–61	58.62	7.80	23.32	2.75	$C_{22}H_{35}B_{10}NO_2$	58.25	7.78	23.83	3.09	444.0	453.6
IVc	86	–	47.69	6.93	26.24	3.02	$C_{16}H_{27}B_{10}NO_4$	47.39	6.71	26.66	3.45	391.5	405.5
IVd	88	–	49.03	7.12	25.35	3.10	$C_{17}H_{29}B_{10}NO_4$	48.67	6.97	25.77	3.34	407.6	419.5
IVe	89	34–35	48.86	7.10	25.42	3.05	$C_{17}H_{29}B_{10}NO_4$	48.67	6.97	25.77	3.34	412.1	419.5
IVf	88	143–144	52.74	5.73	29.10	3.35	$C_{16}H_{21}B_{10}NO_2$	52.30	5.76	29.42	3.81	359.2	367.5
IVg	88	174–175	53.78	6.19	28.06	3.20	$C_{17}H_{23}B_{10}NO_2$	53.52	6.08	28.34	3.67	373.2	381.5
IVh	85	131–132	59.91	5.78	23.95	2.87	$C_{22}H_{25}B_{10}NO_2$	59.57	5.68	24.37	3.16	428.3	443.6
IVi	89	206–207	59.88	5.80	24.01	2.90	$C_{22}H_{25}B_{10}NO_2$	59.57	5.68	24.37	3.16	435.0	443.6
IVj	88	151–152	57.89	5.50	25.29	3.06	$C_{20}H_{23}B_{10}NO_2$	57.53	5.55	25.89	3.35	406.7	417.5
IVk	88	145–146	57.95	5.74	25.54	2.99	$C_{20}H_{23}B_{10}NO_2$	57.53	5.55	25.89	3.35	411.2	417.5
IVl[a]	86	115–116	50.04	5.38	27.68	3.25	$C_{16}H_{20}B_{10}FNO_2$	49.86	5.23	28.05	3.63	369.8	385.4
IVm[b]	87	52–53	43.44	4.65	23.95	2.84	$C_{16}H_{20}B_{10}BrNO_2$	43.05	4.52	24.22	3.14	431.9	446.4
IVn[c]	89	148–149	43.37	4.46	24.10	2.78	$C_{16}H_{20}B_{10}BrNO_2$	43.05	4.52	24.22	3.14	436.1	446.4
IVo[d]	88	160–161	39.20	4.23	21.62	2.55	$C_{16}H_{20}B_{10}INO_2$	38.95	4.09	21.91	2.84	482.0	493.4
IVp[e]	86	207–208	48.52	4.67	21.39	2.43	$C_{20}H_{22}B_{10}BrNO_2$	48.39	4.47	21.78	2.82	481.8	496.4
IVq	87	157–158	50.45	5.68	27.88	3.24	$C_{16}H_{21}B_{10}NO_3$	50.12	5.52	28.19	3.65	372.4	383.5
IVr	88	154–155	52.86	6.19	26.09	3.02	$C_{18}H_{25}B_{10}NO_3$	52.54	6.12	26.27	3.40	403.5	411.5
IVs	88	122–123	57.91	5.64	23.23	2.87	$C_{22}H_{25}B_{10}NO_3$	57.50	5.48	23.53	3.05	443.7	459.6
IVt	87	45–46	52.99	5.73	26.05	3.14	$C_{18}H_{23}B_{10}NO_3$	52.80	5.66	26.40	3.42	397.6	409.5
IVu	86	43–44	54.07	6.10	25.18	3.02	$C_{19}H_{25}B_{10}NO_3$	53.88	5.95	25.53	3.31	415.2	423.5
IVv	88	219–220	49.86	5.03	25.80	2.98	$C_{17}H_{21}B_{10}NO_4$	49.62	5.14	26.27	3.40	422.7	411.5
IVw	89	306–307	49.97	5.25	25.96	3.02	$C_{17}H_{21}B_{10}NO_4$	49.62	5.14	26.27	3.40	423.0	411.5
IVx	85	146–147	52.20	5.96	24.23	2.85	$C_{19}H_{25}B_{10}NO_4$	51.92	5.73	24.60	3.19	429.5	439.5
IVy	85	63–64	54.21	6.18	22.78	2.57	$C_{21}H_{29}B_{10}NO_4$	53.94	6.25	23.12	3.00	449.7	467.6
IVz	89	187–188	52.86	5.24	24.45	6.08	$C_{20}H_{24}B_{10}N_2O_3$	52.52	5.10	24.88	6.45	426.1	434.5
VIIa	53	307–308	62.71	6.28	19.65	2.26	$C_{28}H_{33}B_{10}N_2O_3$	62.32	6.16	20.03	2.60	520.4	539.7
VIIb	59	336–337	62.63	6.22	19.74	2.41	$C_{28}H_{33}B_{10}N_2O_3$	62.32	6.16	20.03	2.60	524.2	539.7

[a] Found F, %: 4.12. Calculated F, %: 4.93. [b] Found Br, %: 17.73. Calculated Br, %: 17.90. [c] Found Br, %: 17.64. Calculated Br, %: 17.90. [d] Found I, %: 25.08. Calculated I, %: 25.72. [e] Found Br, %: 15.76. Calculated Br, %: 16.10.

The IR spectra of carborane aldehyde **III** and azomethines **V** contain the following characteristic absorption bands, ν (cm^{-1}): 3063±2 ($C–H_{carb}$), 2605±5 (B–H), 1758±2 ($C=O_{ester}$), 1595±5, 1500±5, 1415±5 ($C=C_{Ar}$), 1250±10, 1200±10 (C–O), 870±5, 850±5, 830±5, 795±5, 725±5 ($C–H_{Ar}$), 1697 ($C = O_{ald}$), 1633 ± 14 (C=N). In the ^{1}H NMR spectra of *m*-carborane derivatives **III** and **V** there are the characteristic signals of the protons of carborane fragment at δ 3.2 ± 0.1 ppm and aromatic protons at 7.1–8.0 ppm. In the spectrum of carborane aldehyde **III** the signal of CHO-group is observed at δ 10.0 ppm. The ^{1}H NMR spectra of azomethines **Va**–**Vz** contain the signal of HC=N-group at δ 8.5 ± 0.2 ppm, which is characteristic of the Schiff bases of (*E*)-configuration [4].

Azomethines **Vj** and **Vk** were introduced into the reaction with a CH-acid, 5,5-dimethyl-1,3-cyclohexanedione (dimedone) **VI** to give 4-(10,10-dimethyl-8-oxo-7,8,9,10,11,12-hexahydrobenzo[*c*]acridin-7-yl) phenyl (**VIIa**) and 4-(9,9-dimethyl-11-oxo-7,8,9,10,11,12-hexahydrobenzo[*a*]acridin-12-yl)phenyl (**VIIb**) *m*-



VIIa **VIIb**

carboranyl-*C*-carboxylates in 51 and 57% yields relative to the initial dimedone **VI**. The reaction takes place at reflux over 1–2 h.

Under milder conditions, like mixing warm alcoholic solutions of the reagents, the cyclization products precipitate within 24 h. The ease of the cyclization is probably due to a great propensity of 1,3-diketones to enolization. However, the cyclic 1,3-diketones **VI** in anhydrous benzene are mainly in the keto-form, so it is expectable that the reaction rate in benzene would change. Indeed, the formation of hexahydrobenzo[*a*]acridine derivatives occurs only after boiling the reagents in benzene for 3 h. The time of the start of the products formation can easily be determined: they are insoluble in alcohol and benzene, and precipitate in crystalline form from a hot solution. These data demonstrate the dependence of the cyclization process on the enolization degree of 1,3-diketones. In order to increase the yield of the reaction products **VII** and to simplify the procedures of their preparation, we carried out a three-component heterocyclization of *m*-carboranyl-*C*-carboxylate **III** with 1- or 2-naphthylamine (**IVj**, **IVk**) and dimedone **VI**. The reaction was performed by boiling the components in butyl alcohol. Hexahydrobenzo[*a*] acridines **VII** formed under these conditions within 20–30 min with the yields 53% (**VIIa**) and 59% (**VIIb**). As can be seen from the data, the synthesis of benzo[*a*]acridine esters of *m*-carboranyl-*C*-carboxylic acid **VII** through the three-component cyclocondensation was preferable in this case. The hexahydrobenzo[*a*]acridines **VII** are colorless crystalline substances with a distinct melting points (see the table).

A possible mechanism of the three-component cyclocondensation we repeatedly discussed [5, 6]. The most probable course of the reaction is through a stage of the Mannich base formation followed by the rearrangement into 1,5-aminodiketone intermediate, wich undergoes heterocyclization to give products **VII**. The structure of compounds **VII** was confirmed by the IR and ^{1}H NMR spectra.

EXPERIMENTAL

The IR spectra were recorded on a Protégé-460 FTIR-spectrophotometer (Nicolet) from a thin layer or KBr pellets. The ^{1}H NMR spectra were registered on an Avance-500 Bruker spectrometer (500 MHz) from the 10% solutions in chloroform-*d*, the chemical shifts were measured relative to TMS as an internal reference. The molecular weight was determined by the cryoscopy in benzene.

m-Carboranyl-*C*-carboxylic acid chloride **II** was obtained by the reacting of *m*-carboranyl-*C*-carboxylic acid with PCl_5 [7].

4-Formylphenyl *m*-carboranyl-*C*-methanoate (III). To a solution of 0.1 mol of 4-formylphenol **I** and 0.1 mol of *m*-carboranyl-*C*-carboxylic acid chloride **II** in 100 ml of anhydrous benzene was added 0.1 mol of

anhydrous pyridine in 30 ml of benzene within 30 min with cooling to 10–15°C and vigorous stirring. The mixture was stirred for 1 h and diluted with 500 ml of water. The organic layer was separated, washed with water (3×200 ml) and saturated aqueous $NaHCO_3$ solution (2×200 ml), dried over $MgSO_4$, and evaporated. The residue was crystallized from a benzene–hexane mixture.

***m*-Carborane azomethines (Va–Vz).** A solution of 5 mmol of 4-formylphenyl *m*-carboranyl-*C*-methanoate **III** and 5 mmol of the corresponding primary amine **IV** in 40 ml of anhydrous ethanol was boiled for 30–45 min. The solution was cooled to 0–5°C. The azomethine crystals were filtered off, washed with cold methanol, dried in air for 6–8 h. The final purification was performed by the column chromatography on a neutral alumina (40–100 mesh) of II degree of activity by Brockmann. Eluent benzene.

Hexahydrobenzo[*a*]acridine esters of *m*-carboranyl-*C*-carboxylic acid (VIIa, b). *a*. A solution of 0.5 mmol of azomethine **Vj** or **Vk** and 0.5 mmol of dimedone **VI** in 20 ml of butanol was boiled to a precipitate formation (~ 1–2 h). The precipitate was filtered off, washed with hot benzene, and dried.

b. A mixture of 0.35 mmol of 1- or 2-naphthylamine **IVj** or **IVk** and 0.35 mmol of 4-formylphenyl *m*-carboranyl-*C*-methanoate **III** in 20 ml of 1-butanol was boiled for 10 min, the reaction mixture was cooled and mixed with 0.35 mmol of dimedone **VI**. The mixture was heated until the precipitate formation ceased (0.5 h). The precipitate was treated as described above.

IR spectrum, ν, cm^{-1}: 3254±5, 3190±5 (N–H), 3066±2 (C–H_{carb}), 2606±2 (B–H), 1762±2 (C=O_{ester}), 1601±2 (C=$O_{carbonyl}$), 1615±2, 1583±2, 1519±2 (C=C_{Ar}), 1492±2 (N–H), 1252±2, 1203±1 (C–O), 848±3, 815±5, 750±5 (C–H_{Ar}). ^{1}H NMR spectrum, δ, ppm: 0.83 s (3H, CH_3), 1.03 s (3H, CH_3), 2.00 d (1H, CH, ^2J 14 Hz), 2.21 d (1H, CH, ^2J 14 Hz), 2.38 d (1H, CH, ^2J 14 Hz), 2.41 m (10H, $B_{10}H_{10}$), 2.62 d (1H, CH, ^2J 14 Hz), 4.33 s (1H, CH_{carb}), 5.82 s (1H, H^7), 6.92–7.91 m (10H_{Ar}), 9.72 s (1H, NH) (**VIIa**); 0.84 s (3H, CH_3), 1.02 s (3H, CH_3), 2.01 d (1H, CH, ^2J 14 Hz), 2.22 d (1H, CH, ^2J 14 Hz), 2.38 d (1H, CH, ^2J 14 Hz), 2.42 m (10H, $B_{10}H_{10}$), 2.63 d (1H, CH, ^2J 14 Hz), 4.33 s (1H, CH_{carb}), 5.83 s (1H, H^7), 6.90–7.93 m (10H_{Ar}), 9.72 s (1H, NH) (**VIIb**).

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