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# Synthesis of nitriles of the *ortho*-carborane series and their interaction with enaminonitriles

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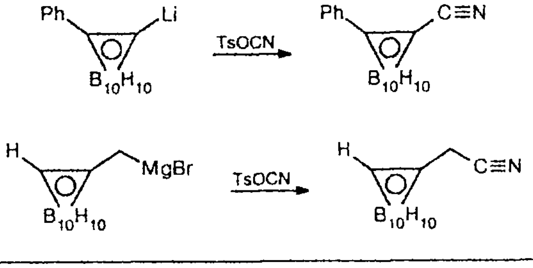
A new convenient method for the synthesis of *o*-carborane carbonitriles by dehydration of carborane carboxamides of the corresponding carboxylic acids with trimethylsilyl polyphosphates was elaborated. Acid-catalyzed reactions of *o*-carborane carbonitriles with enaminonitriles were studied. Thienopyrimidine with a carboranyl substituent was synthesized for the first time.

**Key words:** nitriles of the *o*-carborane series, preparation, reaction with enaminonitriles; thienopyrimidine with a carboranyl substituent, synthesis.

In connection with the use of polyhedral boron compounds in boron neutron-capture therapy of cancer, the synthesis of new organic derivatives of *ortho*-carborane ($C_2B_{10}H_{12}$) is of great interest. Nitriles of the *o*-carborane series are convenient synthons for the synthesis of a wide range of heterocyclic compounds with the goal of creating promising biologically active compounds.

The $RCB_{10}H_{10}C(CH_2)_nCN$ (R = H, Ph, or Me; $n$ = 0, 1, or 2) type nitriles are known.[1–3] Nitriles in which the cyano group and the carborane cage are separated by two methylene groups ($n$ = 2) have been obtained from carboranes and acrylonitrile in good yields.[1] The synthesis of nitriles by dehydration of the corresponding amides under the action of $P_2O_5$ gives low yields in the case of $n$ = 1 and does not occur at all at $n$ = 0.[2] The indicated nitriles result in good yields from the reaction of organolithium or organomagnesium derivatives of carboranes with cyanotosylate (Scheme 1).[3]

**Scheme 1**



However, significant disadvantages of this method are the high price of cyanotosylate and problems associated with its preparation; purification of products by chromatography is also required. Using other cyanating agents, *e.g.*, cyanogen chloride, in a similar reaction leads to a sharp decrease in the yields of nitriles.[4]

The present work is devoted to elaboration of new approaches to the synthesis of nitriles of the *o*-carborane series and their interaction with enaminonitriles.

## Results and Discussion

We elaborated an effective method for the synthesis of $RCB_{10}H_{10}C(CH_2)_nCN$ ($n$ = 0 and 1) type nitriles by dehydration of the corresponding amides with the use of trimethylsilyl polyphosphates, which can be easily obtained from $P_2O_5$ and hexamethyldisiloxane.[5] In this case, nitriles **1** and **2** are formed in high yields from the corresponding readily available carborane amides (Scheme 2).[6]

A possible synthetic application of various nitriles is their reaction with enaminonitriles according to Shishoo—Devani's method (Scheme 3), which leads to pyrimidine derivatives.[7]

We studied the reactions of various nitriles $RCB_{10}H_{10}C(CH_2)_nCN$ ($n$ = 0, 1, and 2) with 2-amino-3-cyano-4,5-tetramethylenethiophene. In the case of nitriles with $n$ = 0 and 1, the reaction does not occur, and the starting compound is recovered from the reaction mixture in quantitative yield. The target product was

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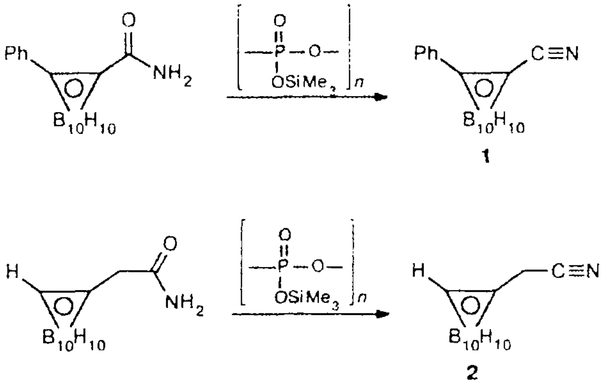
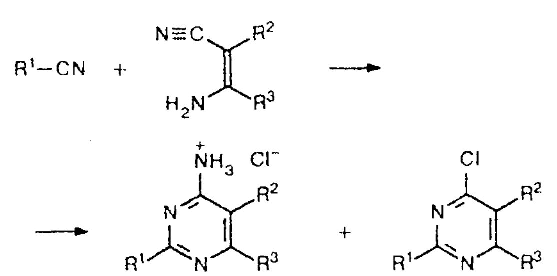
Scheme 2



Scheme 3



obtained only when a nitrile with $n = 2$ was used. The reaction of 1-(2-cyanoethyl)-2-phenyl-*o*-carborane (**4**) with "Gewald thiophene" (**3**) results in a high yield only of aminothienopyrimidine salt **5**, whose neutralization gives aminothienopyrimidine **6** (Scheme 4). No formation of chloro derivative was detected in this reaction.

The structure of compound **5** was determined from its $^1$H NMR spectrum, where, apart from the signals for the CH protons, there is a triplet of protons of the $NH_2^+$ group at δ 3.52 ($J_{^1\text{H}-^{14}\text{N}}$ = 1.6 Hz).

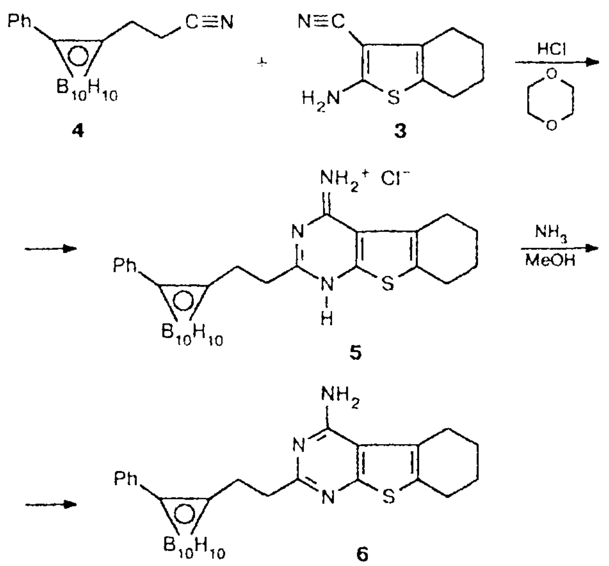
## Experimental

$^1$H and $^{13}$C NMR spectra were obtained on a Bruker AMX-400 instrument (400.13 and 100.61 MHz, respectively) in $CDCl_3$ with tetramethylsilane as the internal standard. Mass spectrum was obtained on a Kratos MS-890 instrument (EI, 70 eV). Melting points were measured using a heating block with an opened capillary.

Aldrich and Fluka chemicals were used for syntheses. Carborane carboxamides[5] and nitrile **3** (see Ref. 3) were synthesized according to the described procedures. Dioxane was distilled over sodium benzophenone ketyl.

**1-Cyano-2-phenyl-*o*-carborane (1).** 2-Phenylcarborane 1-carboxamide (3.4 g, 13 mmol) was added to a solution of trimethyl polyphosphate (55.2 mL) in $CHCl_3$, obtained according to the described procedure[5] from $P_2O_5$ (6.6 g, 23.3 mmol), HMDS (13.3 mL, 83.3 mmol), and $CHCl_3$ (33 mL), and the mixture was refluxed for three days. The

Scheme 4



course of the reaction was monitored by TLC. Then the reaction mixture was poured into water, and the organic phase was separated, washed with water (10×20 mL), and dried over $Na_2SO_4$. The solvent was evaporated, and the product was recrystallized from hexane to give compound **1** (2.82 g, 89%), m.p. 105.0—105.5 °C (Ref. 3: m.p. 104—105 °C). $^1$H NMR, δ: 2.00—4.00 (m, 10 H, BH); 7.25—7.72 (m, 5 H, Ph). $^{13}$C NMR, δ: 59.3 (C—Ph); 84.8 (C—CN); 111.2 (CN); 129.1; 129.2, 130.5, 131.6 (Ph).

**Cyanomethyl-*o*-carborane (2)** was obtained similarly; however, in this case, the duration of the reaction was 6 h. Yield 91%, m.p. 114—115 °C (Ref. 3: m.p. 113—114 °C). $^1$H NMR, δ: 1.50—3.00 (m, 10 H, BH); 3.37 (s, 2 H, $CH_2$); 3.88 (br.s, 1 H, CH of carborane). $^{13}$C NMR, δ: 27.1 (C—CN); 60.0 (CH); 65.0 (C—$CH_2$); 113.3 (CN).

**1-Amino-3-[2-(2-phenyl-*o*-carboran-1-yl)ethyl]-6,7,8,9-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (6).** A mixture of phenylcarboranylpropionitrile (500 mg, 1.83 mmol) and 2-amino-3-cyano-4,5-tetramethylenethiophene (326 mg, 1.83 mmol) was dissolved in dioxane. A flow of dry HCl was passed through the reaction mixture for 8 h. The course of the reaction was monitored by TLC. The solution was then partially evaporated to give after ~2—4 h a precipitate of salt **5**, which was filtered off and dried in air. $^1$H NMR ($CD_3OD$), δ: 2.06, 2.82, 2.94 (m, 8 H, $CH_2$ *cyclo*-$C_6H_8$); 2.61, 3.08 ($A_2B_2$ system, 4 H, $CH_2CH_2$ bridge); 3.52 (t, 1 H, $NH_2^+$); 7.65—7.95 (m, 5 H, Ph). Then, the salt obtained was dissolved in methanol and an excess of an aqueous solution of ammonia was added. The precipitate that formed was filtered off, washed with water, and dried *in vacuo* to give compound **6** (637 mg, 77%). Found (%): C, 52.74; H, 6.41; N, 9.13; S, 6.98. $C_{19}H_{29}B_{10}N_3S$. Calculated (%): C, 53.19; H, 6.47; N, 9.30; S, 7.10. $^1$H NMR, δ: 1.50—3.00 (m, 10 H, BH); 1.89, 2.35, 2.77 (m, 8 H, $CH_2$ *cyclo*-$C_6H_8$); 2.34, 2.90 ($A_2B_2$ system, 4 H, $CH_2CH_2$ bridge); 7.43—7.65 (m, 5 H, Ph). $^{13}$C NMR, δ: 2.3, 22.4, 25.2, 25.9, 32.7, 37.7, 81.8, 83.7, 100.1, 106.3, 113.9, 125.4, 128.8, 130.4, 130.6, 131.1, 133.5, 156.9. MS, *m/z*: 451 [M$^+$].

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