SYNTHESIS OF NOVEL *o*-CARBORANE-BASED KETONITRILES AND THEIR KETO-ENOL TAUTOMERISM

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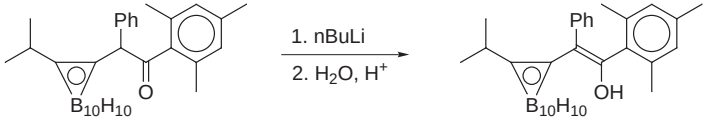
Dedicated to Professor Jaromír Plešek on the occasion of his 75th birthday.

Novel *o*-carborane-based ketonitriles were obtained in enol form *via* acylation of malononitrile with 2-methylcarborane-1-carbonyl chloride as well as by acylation of *o*-carboranylacetonitrile with benzoyl chloride. These ketonitriles appear to exist in solution mostly in enol form.

Keywords: Boranes; Carboranes; *o*-Carborane; Acylation; Malononitrile; Enolization.

One of the main properties of *o*-carboran-1-yl as a substituent is its strong *–I* effect. Thus, electrophilic addition of bromine to 1-vinyl-*o*-carborane proceeds much slower compared to olefins[1]. Still, stabilization of conjugated double bonds also takes place because the *o*-carborane cage has three-dimensional aromatic structure[2]. Therefore, carbonyl derivatives of *o*-carborane are easily enolized due to this effect. The high enolization caused the unusual product formation in the reaction between carboranylacetyl chloride and triethyl phosphite[3]. The enolization of the *o*-carborane derivatives of malonic and acetoacetic ester was determined earlier[4]. Preparation of a stable carboranyl enol has been discussed (Scheme 1), but the results seem to be insufficient[5].



SCHEME 1

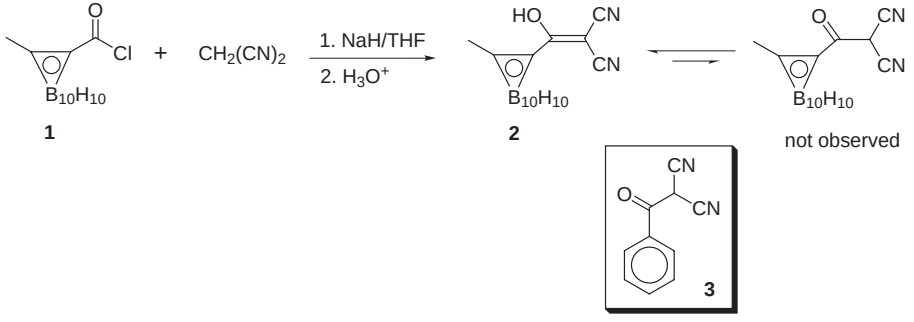
So far the enolized compound has been characterized by ^{1}H NMR and IR spectra, and the ketone only by a poorly resolved IR spectrum. We assume that the ketone must be highly enolized in polar solvents even without lithiation.

Acylated malononitriles are known to be useful synthons for the preparation of various heterocycles[6]. Therefore, synthesis of carborane-based ketonitriles is important for the design of new potential BNCT drugs[7].

In the present paper, we show synthesis and enolization of novel carborane-based ketonitriles and discuss their features.

RESULTS AND DISCUSSION

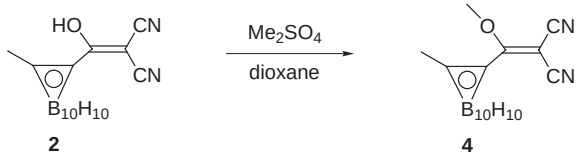
Acylation of malononitrile with 2-methyl-*o*-carborane-1-carbonyl chloride (**1**) was the subject of our investigation. We found that **1** easily acylates malononitrile under standard conditions leading to product **2** (Scheme 2).



SCHEME 2

It was shown[6] (NMR), that benzoylmalononitrile (**3**) exists in the keto form only. In contrast, **2** in solution exists only in the enol form. This was proved by comparison of IR and ^{13}C NMR spectra of **2** and **3**. The signals of two cyano groups were observed in the IR (2 260 and 2 232 cm^{-1}) and ^{13}C NMR (119.6 and 119.5 ppm) spectra of **2**. The ^{1}H NMR spectrum of **2** shows a broad signal of OH at δ 7.90 ppm. In contrast, in the ^{1}H NMR spectrum of **3** in DMSO-d_6, a sharp signal of the –CH(CN)$_2$ proton at δ 4.57 ppm was observed[6]. It is remarkable that **2**, due to its enol structure, is well soluble in water.

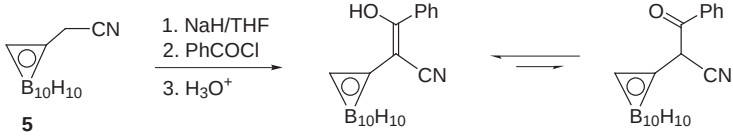
Compound **2** reacts with dimethyl sulfate to yield methylated derivative **4** (Scheme 3).



2 **4**

SCHEME 3

Under the same conditions (see Scheme 1), *o*-carboran-1-ylacetonitrile (**5**) is acylated with benzoyl chloride affording compound **6** (Scheme 4).

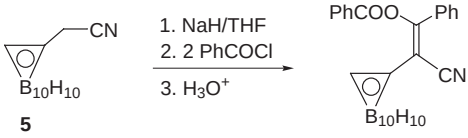


5 **6**

SCHEME 4

The ^1H and ^{13}C NMR data indicate that compound **6** is completely enolized in DMSO and predominantly in acetone. Only three signals were observed in the ^1H NMR spectrum of **6** in DMSO-d_6 (δ 7.52 (5 H, Ph), 5.65 (1 H, CH-carborane) and 3.0–1.4 (10 H, broad, B-H)). The signal of the OH proton is not observed because of its exchange with water. The same spectrum in acetone-d_6 shows the presence of *ca* 10% of the keto form (see Experimental). In the IR spectrum in Nujol, compound **6** was also predominantly enolized. Absorption bands of OH (3 100 cm^{-1}) and C=C (1 617 cm^{-1}) were observed but there was no C=O group band. Unfortunately, we could not determine the *E*,*Z*-configuration of **6**.

Treatment of **5** with 2 equivalents of PhCOCl gave compound **7** in a high yield (Scheme 5).



5 **7**

SCHEME 5

In conclusion, the carborane-based ketonitriles **2** and **6** can be easily prepared in high yields. In solutions they are enolized. Their derivatives **4** and **7** are perspective synthons for further transformations to various compounds.

EXPERIMENTAL

Materials and Equipment

Chemicals were reagent grade and were used as received from standard commercial sources. Compounds **1** and **5** were prepared as described[8]. Melting points were measured in the open capillary and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.61 MHz, respectively, on a Bruker AMX-400 spectrometer. Lock was maintained with deuterated solvents and shifts were referenced to external standards (TMS, deuterated solvents). Chemical shifts are given in ppm (δ-scale). Mass spectra were recorded on a KRATOS MS-890 (70 eV) spectrometer. IR spectra were recorded on a SPECORD M-80 spectrometer in Nujol, wavenumbers are given in cm^{-1}.

1,1-Dicyano-2-hydroxy-2-(2-methyl-*o*-carboran-1-yl)ethene (**2**)

To a stirred solution of $CH_2(CN)_2$ (0.81 g, 12.1 mmol) in absolute THF (20 ml), sodium hydride (1.01 g, 24.2 mmol; 60% suspension in oil) was added at 0 °C and the resulted mixture was stirred for 20 min. Then the solution of **1** (2.5 g, 12.1 mmol) in absolute THF (20 ml) was added dropwise, so that temperature remained between 5–10 °C. The mixture was allowed to reach room temperature and 50 ml of water was added. Then it was washed with 2 × 50 ml of Et_2O and 50 ml of hexane. The water layer was acidified to pH 1 and extracted with 6 × 25 ml of Et_2O. The ether fractions were dried with anhydrous Na_2SO_4, the solvent was distilled off and the product was recrystallized from chloroform to yield 2.3 g (75%) of **2**; m.p. 186 °C. For $C_7H_{14}B_{10}N_2O$ calculated: 33.59% C, 5.64% H, 11.19% N; found: 33.09% C, 5.22% H, 10.93% N. ^{1}H NMR (acetone-d_6): 7.90 (broad s, 1 H, OH); 2.12 (s, 3 H, CH_3); 3.30–1.05 (m, 10 H, BH). ^{13}C NMR (acetone-d_6): 173.8 (HO-C=); 119.6, 119.5 (CN); 81.2 (C(carb)-C=C); 76.9 (C$(CN)_2$); 53.4 (C(carb)-CH_3); 23.3 (CH_3). MS (*m/z*): 250 (M^+). IR: 3 520 (OH); 2 587 (BH); 2 260, 2 232 (CN); 1 605 (C=C).

1,1-Dicyano-2-methoxy-2-(2-methyl-*o*-carboran-1-yl)ethene (**4**)

To a suspension of Na_2CO_3 (5 g) in dioxane (12 ml) and water (2 ml) the solution of **2** (1.87 g, 7.5 mmol) and dimethylsulfate (5 ml) in dioxane (10 ml) were added dropwise and then the mixture was refluxed for 2.5 h. Afterwards, 60 ml of water was added and the mixture was extracted with 3 × 50 ml of ether. The ether fractions were combined, dried over anhydrous Na_2SO_4, the solvents were evaporated and the product was recrystallized from benzene to yield 1.58 g (81%) of **4**; m.p. 124 °C. For $C_8H_{16}B_{10}N_2O$ calculated: 36.35% C, 6.10% H, 10.60% N; found: 35.92% C, 6.01% H, 10.20% N. ^{1}H NMR (acetone-d_6): 3.59 (s, 3 H, CH_3-O); 2.07 (s, 3 H, CH_3(carb)); 3.30–1.05 (m, 10 H, BH). ^{13}C NMR (acetone-d_6): 169.1 (MeO-C=); 116.4, 115.8 (CN); 81.9 (C(carb)-C=C); 78.0 (C$(CN)_2$); 68.1 (C(carb)-CH_3); 65.9 (CH_3-O); 23.2 (CH_3(carb)). MS (*m/z*): 266 (M^+).

1-(*o*-Carboran-1-yl)-2-hydroxy-2-phenylacrylonitrile (**6**)

To a stirred solution of **5** (0.915 g, 5 mmol) in absolute THF (30 ml), sodium hydride (0.4 g, 10.2 mmol; 60% suspension in oil) was added at 0 °C and the resulting mixture was stirred for 30 min. Then a solution of benzoyl chloride (0.7 g, 5 mmol) in absolute THF (20 ml) was added dropwise, so that temperature of the reaction mixture remained between 5–10 °C. To

the resulting mixture, 1 M HCl (50 ml) was added, the organic layer was separated and the water layer was washed with 5 × 15 ml THF. The organic layers were combined, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The product was then dissolved in THF (5 ml) and precipitated by addition of hexane (5 ml) to yield 1.13 g (82%) of **6**; m.p. 173 °C (dec). For $C_{11}H_{17}B_{10}NO$ calculated: 45.98% C, 5.96% H, 4.87% N; found: 45.67% C, 5.91% H, 4.93% N. ^{1}H NMR (acetone-d_6): Enol form (*ca* 90%): 11.71 (broad s, 1 H, OH); 7.55 (m, 5 H, Ph); 5.40 (broad s, 1 H, CH(carb)). Keto form (*ca* 10%): 8.15 (d, 2 H, *o*-Ph); 7.82 (d, 1 H, *p*-Ph); 7.68 (t, 2 H, *m*-Ph); 6.29 (s, 1 H, CH-CN); 5.03 (broad s, 1 H, CH(carb)). ^{13}C NMR (DMSO-d_6): 171.4 (C-OH); 134.2, 131.7, 130.0, 129.6 (Ph); 118.0 (CN); 84.1 (=C-CN); 70.7 (C(carb)); 61.2 (HC(carb)). IR: 3 100 (OH); 2 590 (BH); 2 225 (CN); 1 617 (C=C).

2-Benzoyloxy-1-(*o*-carborane-1-yl)-2-phenylacrylonitrile (**7**)

To a stirred solution of **5** (0.915 g, 5 mmol) in absolute THF (30 ml), sodium hydride (0.4 g, 10.2 mmol; 60% suspension in oil) was added at 0 °C and the resulting mixture was stirred for 30 min. Then a solution of benzoyl chloride (1.4 g, 10 mmol) in absolute THF (20 ml) was added dropwise, so that temperature of the reaction mixture remained between 5–10 °C. To the resulting mixture, water (50 ml) was added, the organic layer was separated and the water layer was washed with 6 × 30 ml Et_2O. The organic layers were combined, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The product was recrystallized from hexane to yield 1.7 g (89%) of **6**; m.p. 207 °C. For $C_{18}H_{21}B_{10}NO_2$ calculated: 55.23% C, 5.41% H, 3.58% N; found: 55.01% C, 5.37% H, 3.51% N. ^{1}H NMR ($CDCl_3$): 8.07–7.43 (m, 10 H, 2 Ph); 4.33 (broad s, 1 H, CH(carb)). ^{13}C NMR ($CDCl_3$): 166.1 (CO); 162.4 (=C-O); 137.8, 135.0, 132.2, 130.5, 129.5, 129.1, 128.8, 128.1, 127.0 (aromatics); 115.5 (CN); 98.6 (=CCN); 67.2 (C(carb)); 61.4 (HC(carb)). IR: 2 605 (BH); 2 218 (CN); 1 751 (C=O); 1 614 (C=C).

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