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A new approach to incorporate the carboranyl fragment into 2,5-diazabicyclo[2.2.2]oct-2-enes†

Gennady L. Rusinov,*[a] Egor V. Verbitsky,[a] Pavel A. Slepukhin,[a] Olga N. Zabelina,[a] Il'ya N. Ganebnykh,[a] Valery N. Kalinin,[b] Valentina A. Ol'shevskaya[b] and Valery N. Charushin[a]

[a] *I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620041 Ekaterinburg, Russian Federation. Fax: +7 343 374 1189; e-mail: rusinov@ios.uran.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5085; e-mail: vkalin@ineos.ac.ru*

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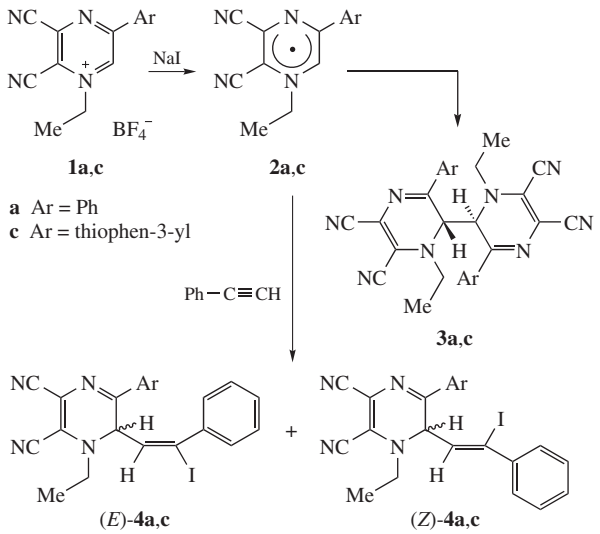
5-(Het)aryl-2,3-dicyano-1-ethylpyrazinium salts have been established to react with 9-allyl-*ortho*- and 9-allyl-*meta*-carboranes in the presence of sodium iodide into carboranylmethyl derivatives of 2,5-diazabicyclo[2.2.2]oct-2-ene.

Compounds bearing the carboranyl fragment are of interest as building blocks in the design of photo- and radiosensitive pharmaceuticals for the boron neutron capture therapy (BNCT) of cancer.[1] On the other hand, 2,5-diazabicyclo[2.2.2]octanes and other bridged piperazines belong to the family of pharmacologically active compounds.[2] Here we suggest a new approach to incorporate the carboranyl fragment into 2,5-diazabicyclo-[2.2.2]oct-2-enes.

We have recently shown that treatment of 1-ethyl-5-(het)aryl-2,3-dicyanopyrazinium salts **1a**,**c** with sodium iodide results in the formation of the radical species **2**, which either undergo dimerization into bipyrazinyls **3a**,**c** or can be trapped with acetylenes to form a mixture of *Z*- and *E*-pyrazinyl iodoalkenes **4a**,**c** (Scheme 1).[3]

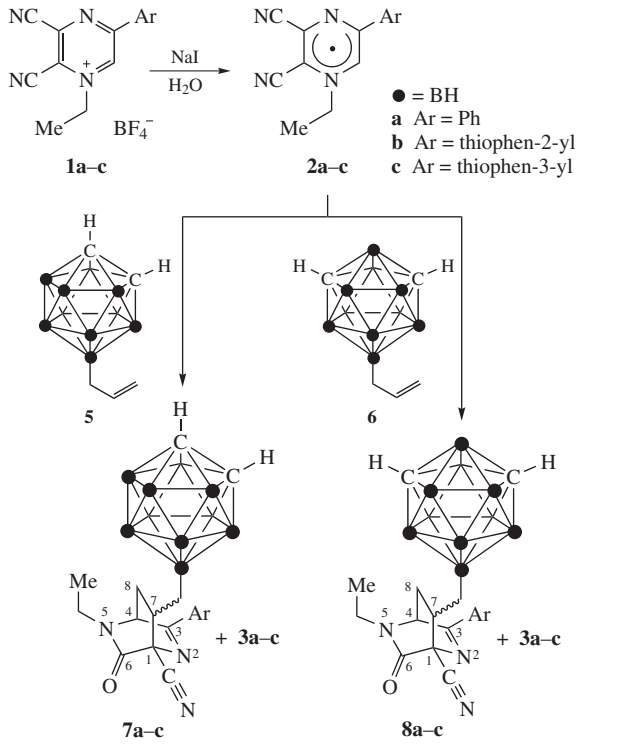


Scheme 1

Attempts to trap pyrazinyl radicals **2** with compounds bearing the C–C double bond, such as 9-allyl-*ortho*- and 9-allyl-*meta*-carboranes **5** and **6**, resulted in the formation of 2,5-diazabicyclo[2.2.2]oct-2-en-1-carbonitriles **7** and **8** (Scheme 2).

Although the mechanism has not been studied in detail, the reaction appears to run through intermediate radical species. The formation of radical intermediates **2a–c** is substantiated by the formation of their dimeric molecules **3a–c** in 41–59% yields.

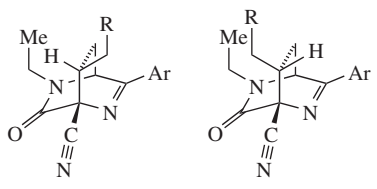
† Dedicated to Academician O. N. Chupakhin on his 75th anniversary.



Scheme 2

Compounds **7a–c**‡ and **8a–c**§ were isolated by preparative HPLC as a mixture of two stereoisomers with (*S*) **A** and (*R*) **B** configurations of the C(7) chiral centre.

Structural elucidations of 2,5-diazabicyclo[2.2.2]oct-2-ene-1-carbonitriles **7a–c** and **8a–c** have been performed by ^{1}H NMR spectroscopy‡,§ and X-ray analysis (Figure 1).¶ The yields of products **7a–c** and **8a–c** and the ratios of diastereomers are given in Table 1.



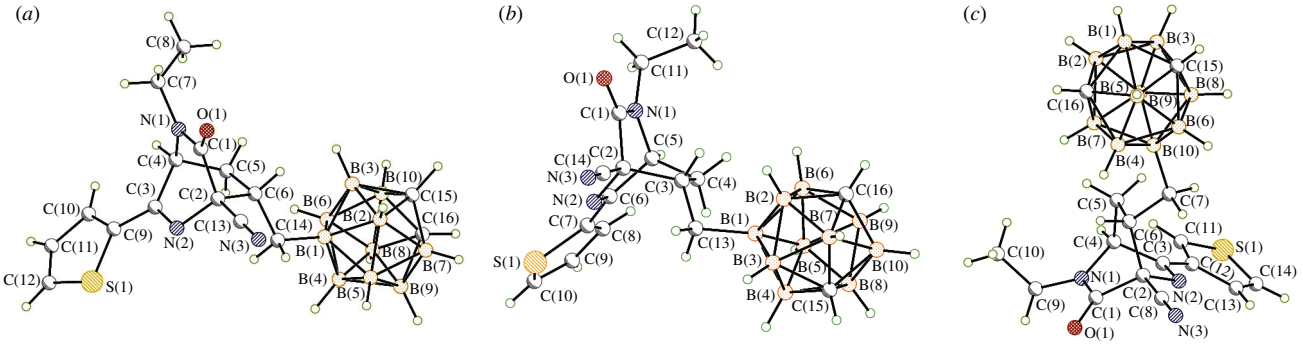


Figure 1 X-ray crystal structures of compounds (*a*) **7b** (**A**), (*b*) **8b** (**A**) and (*c*) **8c** (**A**).

‡ All solvents and reagents were purified and prepared according to the published procedures.[9] Compounds **1a–c** were synthesized as described elsewhere.[8]

All microwave experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 300 W maximum power. The reactions were carried out in microwave process vials (10 ml) sealed Teflon crimp top, which can be exposed to 250 °C and 20 bar internal pressure. The temperature was measured with an IR sensor on the outer surface of the process vial.

Preparative HPLC was performed with ZORBAX Eclipse XDB-C18 PrepHT (21.2×150 mm, 5 μm) column, with flow rate of 20 ml min^{-1}. Mixture of MeCN–H_2O (7:3) was used as a mobile phase. The ^{1}H NMR spectra were recorded on a Bruker DRX-400 instrument (400 MHz) with TMS as the internal standard. Mass spectra were measured on a Shimadzu LCMS-2010 quadrupole liquid GLC mass spectrometer in MeCN at a scan rate of 0.25 ml min^{-1} using a Supelco LC-18 column (4.6×250 mm). Mass spectra were obtained both in positive and negative modes with APCI and ESI probe installed. Quadrupole array and curved desolvation line (CDL) were used in scan-mode according to the parameters stored in the auto-tune file. Nebulizing gas was nitrogen, at a flow rate of 2.5 dm^3 min^{-1}. The probe voltage was 4.5 kV. IR spectra were obtained using a Perkin–Elmer Spectrum One B Fourier transform infrared spectrometer (FT-IR). The elemental analysis was carried out on an automated Perkin–Elmer PE-2400 analyzer. The melting points were determined on a combined Boetius hot-stage apparatus and are uncorrected. Flash chromatography was performed using silica gel (0.040–0.063 mm, 230–400 mesh). The course of the reactions was monitored and the purity of the products was checked by TLC on Silufol UV-254 plates (Russia); the spots were visualized with iodine vapour and UV radiation.

Typical procedure for the synthesis of compounds **7a–c**. Sodium iodide (0.6 mmol) was added to a solution of salt **1a** (**1b** or **1c**) (0.5 mmol) and 9-allyl-*ortho*-carborane **5** (0.5 mmol) in dry MeCN (7 ml). After 35 min of stirring at room temperature a precipitate of dimer **3a** (**3b** or **3c**) was filtered off, washed with acetonitrile (3×5 ml) and water (3×5 ml). Filtrate was distilled off under reduced pressure and the residue was purified on silica gel using $CHCl_3$. The obtained mixture of diastereomers was separated by preparative HPLC with MeCN–H_2O (45:55). For yields of compounds **7a–c**, see Table 1.

5-Ethyl-6-oxo-3-phenyl-7-(1,2-dicarba-closo-*dodecarboran-9-ylmethyl-2,5-diazabicyclo[2.2.2]oct-2-ene-1-carbonitrile* **7a**. Beige crystal powder, mp 218–223 °C. HPLC, t_R 4.9–6.0 min. In the ^{1}H NMR spectrum two sets of signals corresponding to major (**A**) and minor (**B**) diastereomers of **7a** were observed. ^{1}H NMR ($CDCl_3$) δ: isomer **A**: 0.56 (m, 1H, CH), 1.11 (t, 3H, Me, *J* 7.2 Hz), 1.19–2.90 (m, 15H, BH, CH, 2CH_2, C^{8}H), 3.30–3.40 (m, 1H, NCH_A), 3.52–3.60 (m, 1H, NCH_B), 4.83 (m, 1H, C^{4}H), 7.47–7.58 (m, 3H, Ph), 7.85–7.88 (m, 2H, Ph); isomer **B**: 0.56 (m, 1H, CH), 1.12 (t, 3H, Me, *J* 7.2 Hz), 1.19–2.90 (m, 15H, BH, CH, 2CH_2, C^{8}H), 3.30–3.40 (m, 1H, NCH_A), 3.52–3.60 (m, 1H, NCH_B), 4.83 (m, 1H, C^{4}H), 7.47–7.58 (m, 3H, Ph), 7.85–7.88 (m, 2H, Ph). LC/MS (APCI, in MeOH, Q-array scan), *m*/*z* [*I*(%), positive region]: 410 [M]$^+$ (99), 411 [M + H]$^+$ (100), 442 [M + MeOH]$^+$ (78), 443 [M + H + MeOH]$^+$ (65); *m*/*z* [*I*(%), negative region]: –408 [M – 2H]$^-$ (27), –409 [M – H]$^-$ (81), –410 [M]$^-$ (100). Found (%): C, 52.92; H, 6.67; N, 10.13. Calc. for $C_{18}H_{27}N_3OB_{10}$ (%): C, 52.79; H, 6.64; N, 10.26.

For characteristics of compounds **7b**,**c**, see Online Supplementary Materials.

In case of compound **7b**, the major isomer was isolated by preparative HPLC and its absolute configuration (**A**) was determined by X-ray analysis (Figure 1). Absolute configurations and ratio of diastereoisomers **A** and **B** for compounds **7a**,**c** and **8a–c** were established by comparison of their ^{1}H NMR spectroscopy and X-ray analysis data with those for compound **7b**.

It is noteworthy that the yields of 2,5-diazabicyclo[2.2.2]oct-2-ene-1-carbonitriles **7** and **8** can be increased. Indeed, the

§ *Typical procedure for the synthesis of compounds* **8a–c**. Sodium iodide (0.6 mmol) was added to a solution of salt **1a** (**1b** or **1c**) (0.5 mmol) and 9-allyl-*meta*-carborane **6** (0.5 mmol) in dry MeCN (7 ml). After 35 min of stirring at room temperature the resulting precipitate of dimer **3a** (**3b** or **3c**) was filtered off, washed with acetonitrile (3×5 ml) and water (3×5 ml). Filtrate was distilled off under reduced pressure and the residue was purified on silica gel using $CHCl_3$. The obtained mixture of stereoisomers was separated by preparative HPLC. For yields of compounds **8a–c**, see Table 1.

5-Ethyl-6-oxo-3-phenyl-7-(1,7-dicarba-closo-*dodecarboran-9-ylmethyl-2,5-diazabicyclo[2.2.2]oct-2-ene-1-carbonitrile* **8a**. Beige crystal powder, mp 164–166 °C. HPLC, t_R 5.5–6.6 min. In the ^{1}H NMR spectrum two sets of signals corresponding to major (**A**) and minor (**B**) diastereomers of **8a** were observed. ^{1}H NMR ($CDCl_3$) δ: isomer **A**: 0.71 (m, 1H, CH), 1.13 (t, 3H, Me, *J* 7.2 Hz), 1.25–2.90 (m, 15H, BH, CH, 2CH_2, C^{8}H), 3.32–3.42 (m, 1H, NCH_A), 3.54–3.63 (m, 1H, NCH_B), 4.88 (dd, 1H, C^{4}H, *J* 3.7 Hz, *J* 2.0 Hz), 7.49–7.59 (m, 3H, Ph), 7.89–7.92 (m, 2H, Ph); isomer **B**: 0.71 (m, 1H, CH), 1.14 (t, 3H, Me, *J* 7.2 Hz), 1.25–2.90 (m, 15H, BH, CH, 2CH_2, C^{8}H), 3.41–3.50 (m, 1H, NCH_A), 3.54–3.63 (m, 1H, NCH_B), 4.90 (dd, 1H, C^{4}H, *J* 2.3 Hz, *J* 3.3 Hz), 7.49–7.59 (m, 3H, Ph), 7.89–7.92 (m, 2H, Ph). LC/MS (ESI, in MeCN, Q-array scan), *m*/*z* [*I*(%), positive region]: 410 [M]$^+$ (9), 411 [M + H]$^+$ (16), 412 [M + 2H]$^+$ (15); *m*/*z* [*I*(%), negative region]: –408 [M – 2H]$^-$ (25), –409 [M – H]$^-$ (16), –410 [M]$^-$ (25). Found (%): C, 52.56; H, 6.62; N, 10.23. Calc. for $C_{18}H_{27}N_3OB_{10}$ (%): C, 52.79; H, 6.64; N, 10.26.

For characteristics of compounds **8b**,**c**, see Online Supplementary Materials.

¶ *Crystallographic data for* **7b**, **8b** *and* **8c**.

Crystals of **7b** were obtained by recrystallization from acetone, orthorhombic, space group *Pbca*; unit cell parameters: a = 11.887(4), b = = 14.523(3) and c = 26.204(4) Å, V = 4523.7(18) Å^3, Z = 8. The final R factor was 0.0506 [$wR(F^2)$ = 0.0808] for 1565 reflections $F_0 > 2\sigma(I)$.

Crystals of **8b** were obtained by recrystallization from acetone, orthorhombic, space group *Pbca*, unit cell parameters: a = 12.0399(5), b = = 18.4749(9) and c = 20.3770(10) Å, V = 4532.6(4) Å^3, Z = 8. The final R factor was 0.0452 [$wR(F^2)$ = 0.0615] for 1880 reflections $F_0 > 2\sigma(I)$.

Crystals of **8c** were obtained by recrystallization from acetone, orthorhombic, space group *Pbca*, unit cell parameters: a = 11.9647(9), b = = 18.4997(9) and c = 20.3203(16) Å, V = 4497.8(5) Å^3, Z = 8. The final R factor was 0.0389 [$wR(F^2)$ = 0.0796] for 2382 reflections $F_0 > 2\sigma(I)$.

X-ray diffraction analysis on single crystals was performed on an X-ray diffractometer X-calibur-3 equipped with a CCD detector [φ- and ω-scanning, λ(MoKα) radiation, graphite monochromator]. The structure was solved by the direct method using the SHELXS-97 and refined applying the SHELXL-97 program packages.[10]

CCDC 738688, 738689 and 738690 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2009.

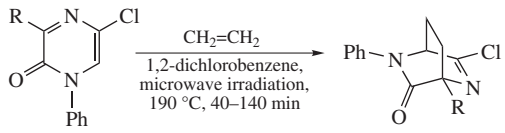
Table 1 Yields of compounds **3a–c**, **7a–c** and **8a–c**, and ratio of stereoisomers for compounds **7** and **8**.[a]

Reaction	Products (yields, %)	Ratio of stereoisomers **A**:**B** after HPLC separation
1a + **5**	**3a** (49) + **7a** (29)	9:1
1b + **5**	**3b** (45) + **7b** (21)	4:1
1c + **5**	**3c** (41) + **7c** (12)	6:1
1a + **6**	**3a** (59) + **8a** (17)	9:1
1b + **6**	**3b** (30) + **8b** (21)	9:1
1c + **6**	**3c** (41) + **8c** (8)	4:1

[a]According to ^{1}H NMR spectroscopy data in all cases, the ratios of stereoisomers **A**:**B** in reaction mixtures were approximately 1:1.

reaction of **1c** with a five-fold excess of 9-allyl-*ortho*-carborane **5** gave 2,5-diazabicyclo[2.2.2]oct-2-ene-1-carbonitrile **7c** in 36% yield, while yield of dimer **3c** fell down to 14%.

Data concerning the synthesis of 2,5-diazabicyclo[2.2.2]oct-2-enes **10a**,**b** by the Diels–Alder reaction of 2(1*H*)-pyrazinones **9a**,**b** are available[4–6] (Scheme 3).



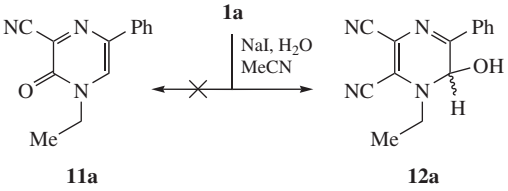
9a,**b** **10a**,**b**

a R = CN
b R = Cl

Scheme 3

Taking into account these data, we were obliged to elucidate the ability of the pyrazinone azadiene system to undergo a cycloaddition reaction with allylcarboranes. We have established that 2(1*H*)-pyrazinone[7] **11a**[††] does not react with 9-allyl-*ortho*-carborane **5** under the reaction conditions (MeCN, 25 °C, 24 h), both in the presence or without sodium iodide. Attempts to detect the formation of 2(1*H*)-pyrazinone **11a** in the reaction mixture of **1a** with sodium iodide by TLC failed, and no traces of 2(1*H*)-pyrazinone **11a** in the reaction mixtures were found. Instead, the reaction of salt **1a** with an aqueous solution of sodium iodide gave 1,2-dihydropyrazine **12a**[8] (Scheme 4).

We have found that 2(1*H*)-pyrazinones **11a**,**c** undergo a cycloaddition reaction with 9-allyl-*ortho*-carborane **5**; however, it takes place under severe hard conditions (microwave irradiation, 1,2-dichlorobenzene, 195 °C, 5 h) to give corresponding



11a **12a**

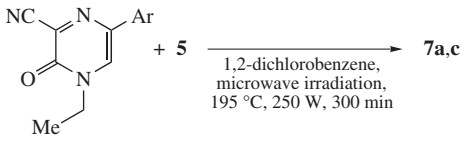
Scheme 4

[††] *General procedure for the synthesis of pyrazinones*[7] **11a**,**c**. Bis(pyridine)iodonium tetrafluoroborate[11] (2.2 mmol) was added to a solution of compound **12a**[8] (or **12c**) (1.0 mmol) in dry MeCN (7 ml). The reaction mixture was stirred for 24 h, evaporated, and the residue was subjected to chromatography on silica gel (eluent ethyl acetate–hexane, 1:1).

For characteristics of compounds **11a**,**c**, see Online Supplementary Materials.

General procedure for the synthesis of cycloadducts **7a**,**c** *from pyrazinones* **11a**,**c** *by microwave irradiation*. A solution of the corresponding 2(1*H*)-pyrazinone **11a**,**c** (0.3 mmol) and 9-allyl-*ortho*-carborane **5** (0.9 mmol) in 1,2-dichlorobenzene (5 ml) was irradiated at 195 °C (250 W) for 300 min. Experiments were carried out in a 10 ml sealed microwave process vial. The reaction mixture was worked up by evaporating the 1,2-dichlorobenzene, and a crude product was purified by preparative HPLC. Both cycloaddition products **7a**,**c** were identified by comparison of their ^{1}H NMR spectra with those of authentic materials.

2,5-diazabicyclo[2.2.2]oct-2-enes **7a**,**c** as a mixture of two stereoisomers **A** and **B** (Scheme 5). Note that, in this reaction, the formation of isomer **B** is predominant in cycloaddition products.



11a,**c**

	Yield (%)	Ratio of stereoisomers **A**:**B** after HPLC separation
7a	19	1:1.6
7c	12	1:1.5

Scheme 5

Although the reaction mechanism is still not clear, the radical nature of the reaction of salts **1a–c** with 9-allylcarboranes **5** and **6** at room temperature appears to be a reasonable explanation, contrary to intermediacy of pyrazinones requiring hard reaction conditions.

In conclusion, note that 1-ethyl-5-(het)aryl-2,3-dicyanopyrazinium salts undergo single-electron reduction by the action of sodium iodide, thus generating pyrazinyl radicals, which react with allylcarboranes to give 2,5-diazabicyclo[2.2.2]oct-2-enes bearing carboranyl substituent.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2009.09.002.

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