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An efficient synthesis of carboranyl tetrazoles via alkylation of 5-R-1H-tetrazoles with allylcarboranes

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ABSTRACT

An efficient triflic acid catalyzed regioselective alkylation of 5-R-1H-tetrazoles with readily available allylcarboranes is reported. The suggested synthetic procedure allows the formation of a variety of carboranyl-substituted tetrazoles in a good yield under mild conditions. Transformations of newly synthesized carboranyl tetrazoles under UV irradiation were studied. Allylcarboranes as starting materials were prepared via Pd-catalyzed cross-coupling reaction of iodocarboranes with allylmagnesium bromide.

1. Introduction

Tetrazoles, an important class of nitrogen-rich heterocycles, demonstrate a wide range of applications in different fields including organic synthesis, drug development, materials sciences, and coordination chemistry [1]. Tetrazoles have been most extensively investigated by medicinal chemists [2,3]. Substituted tetrazoles are known to possess antibacterial [4], antifungal [5], antiviral [6], analgesic [7,8], anti-inflammatory [9], antiulcer [10] and antihypertensive [11] activities. In particular, some tetrazole derivatives were found to be promising anticancer agents that bind DNA, form stable complexes and may act as DNA damaging chemotherapeutics [12–14]. In drug design, tetrazoles are used in pharmaceuticals as lipophilic spacers and non-classical surrogates for the carboxylic acid group and *cis*-amide bond because tetrazoles' planarity and acidity are similar to carboxylic acids. However, the tetrazole function is metabolically more stable at physiological pH [15–17] than that of the carboxylic group; therefore, clearance of a tetrazole based drug might be longer. Furthermore, toxic properties of a drug can decrease after the introduction of a tetrazole ring into the molecule [18]. Several tetrazole derivatives are also used in agriculture as plant growth regulators, herbicides and fungicides [19].

Due to a high enthalpy of formation, tetrazole decomposition results in the liberation of two nitrogen molecules and a significant amount of energy. Therefore, tetrazole derivatives have been explored as high energy compounds [20–22]. Other applications of tetrazole moieties include their wide use in synthetic organic chemistry as important precursors of five-membered nitrogen-containing heterocycles [23–26], ligands in coordination chemistry (due to their sensitivity and selectivity to metal ions [27–29]), and natural products [30–36].

The diversity and importance of practical application of tetrazole heterocycles stimulated efforts to find new types of molecules and to provide an excess to libraries of compounds from available and versatile precursors. The most interesting compounds containing tetrazole moieties are 5-substituted tetrazoles. Various methodologies for preparation of compounds with a tetrazole ring system have been developed and reviewed [37]. Among them are azide and nitrile [2 + 3] cycloaddition reactions [38–48]. Sodium azide is usually used as the azide source, although silicon [49], tin [50] and organoaluminum azides [51] also have been explored. Most nitriles react well in this cycloaddition, although sterically unhindered and electron-deficient aryl nitriles give the greatest yields [52,53]. Multicomponent Passerini and Ugi reactions have been exploited to obtain compounds with a tetrazole ring system within a short reaction time with good overall yields [54–57]. Functionalization of synthetic intermediates that already contain the tetrazole fragment is an alternative and powerful approach used for the preparation of tetrazole compounds [58,59].

On the other hand, there is a growing interest in the derivatization of icosahedral carboranes with nitrogen heterocycles [60] which are promising objects in medicinal chemistry [61],

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photochemistry [62–69] and functional materials [70]. Recently we have reported the possibility of using the methodology of 1,3-dipolar cycloaddition (the 'click' reaction) to modify the *closo*-carborane polyhedron, $C_2B_{10}H_{12}$, with 1,2,3-triazole heterocycles starting from 1-azidomethyl-*o*-carborane and terminal alkynes [71,72]. Central in this study was the preparation of 1-azidomethyl-*o*-carborane [71]. However, we failed to prepare 5-substituted carborane 1H-tetrazoles based on azide and nitrile [2 + 3] cycloaddition approach [73,74], and no reaction was observed for 1-azidomethyl-*o*-carborane and nitriles. We have shown that carborane tetrazoles can be synthesized by direct introduction of the tetrazole fragment into the carborane polyhedra through the acylation of 5-phenyl tetrazole with carborane carboxylic acid chlorides [75]. Therefore, in continuation of our efforts towards the preparation of diverse carborane tetrazoles through the direct introduction of tetrazole moiety to the carborane polyhedron we here report the synthesis of novel series of carborane tetrazoles via the alkylation of 5-R-1H-substituted tetrazoles with easily accessible boron-substituted allylcarboranes [76,77]. We took advantage of these compounds as they are readily available from common starting materials through selective palladium catalyzed cross-coupling reaction of corresponding iodocarboranes [60] with allylmagnesium halides.

2. Experimental

2.1. General information

All solvents were freshly distilled from appropriate drying agents before use. Other reagents were recrystallized or distilled if necessary. Reactions were performed in the atmosphere of dry argon. The purity of newly synthesized compounds was tested by TLC on Sorbfil. Eluents: hexane for compounds **3**, **4**, **13**, $CHCl_3$–hexane (4:1) for **5**–**8**, **10**, **11**, **14**–**16** and $CHCl_3$ for **21**, **22**. IR spectra were registered on a Brucker FIR spectrometer Tensor 37 in KBr tablets. UV-irradiation of compounds **5**, **7**, **14**, **15** was carried out with a UV mercury lamp (GL1/T6 8 W, λ_{max} = 254 nm). NMR spectra were recorded on a Bruker Avance-400 spectrometer operating at 400 MHz for ^{1}H, 128.28 MHz for ^{11}B, 150.93 MHz for ^{13}C. Chemical shifts were relative to TMS for ^{1}H, and ^{13}C, $BF_3.OEt_2$ for ^{11}B. The solvent was $CDCl_3$. 2D gradient selected ^{1}H–^{15}N HMBC experiment for compound **5** was recorded on a 600 MHz Bruker spectrometer (^{1}H: 600.22 MHz; ^{15}N: 60.83 MHz) using a 5 mm Broadband probe with z-gradient; the spectral widths of ^{1}H and ^{15}N dimensions were 6 and 30 kHz, respectively; 16 scans were acquired for each t1 increment with total 128 increments; 100 ms was used for the evolution time of J_{NH} couplings (5 Hz). Data was processed with zero-filling on F1 and F2 dimension. The ^{15}N chemical shifts were measured relative to neat CH_3NO_2. Single crystal X-ray analysis: crystals of **5** (colourless prisms, $C_{12}H_{22}B_{10}N_4$, M = 330.43) are monoclinic, space group $P2_1/n$, at 110 K: a = 10.313(2), b = 9.1922(18), c = 18.761(4) Å, β = 95.89(3)°, V = 1769.1(6) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.241 g cm^{-3}, μ(Mo Kα) = 0.67 cm^{-1}, F(000) = 688. Intensities of 11514 reflections were measured with a Smart APEX II CCD diffractometer [λ(Mo Kα) = 0.71072 Å, ω-scans, $2\theta < 58°$] and 4676 independent reflections (R_{int} = 0.0306) were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in an anisotropic-isotropic approximation. The hydrogen atoms of the carborane moiety were located from the Fourier density synthesis and refined in isotropic approximation. For all other hydrogen atoms the positions were calculated, and they were refined in a riding model. The refinement converged to wR_2 = 0.1268 and GOF = 1.042 for all independent reflections (R_1 = 0.0455 was calculated against F for 3793 observed reflections with $I > 2\sigma(I)$). All calculations were performed using SHELXTL PLUS [78]. CCDC 1456831 contains the supplementary crystallographic data. General method was used to prepare aryl tetrazoles **1**, **2** and **9** from corresponding nitriles [52,53].

2.2. General procedure for preparation of allylcarboranes (*3*, *4*)

To a mixture of 9-iodo-*m*-carborane or 9-iodo-*o*-carborane (10.8 g, 40 mmol) and $(PPh_3)_2PdCl_2$ (0.15 g, 0.2 mmol) in ether (100 mL) allyl magnesium bromide (60 mmol, 41.7 mL, 1.44 M solution) was added dropwise with an extensive stirring in argon atmosphere. The resulting mixture was refluxed for 6–8 h until TLC (eluent heptane) indicated complete disappearance of the corresponding iodocarborane. After the completion of the reaction hydrochloric acid (25 mL, 1.6 N) was added dropwise to the reaction mixture. Organic layer was separated and washed with water, sat. aq $Na_2S_2O_3$ solution (50 mL) and dried over $MgSO_4$. After removal of solvent, the crude product was purified by column chromatography on a silica gel with heptane as an eluent to afford corresponding allylcarboranes in a quantitative yield.

2.2.1. 9-Allyl-m-carborane (*3*)

Yield: 6.1 g (97%). Colorless oil. B.p. 78–79 °C/1 mmHg[76]. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.95 (ddt, 1H, J = 16.9, 9.89, 7.89 Hz, =**CH**–CH_2–B^9), 4.88 (dt, 1H, J = 17.2, 1.15 Hz, CH_2–CH=**CH_2**-*trans*), 4.82 (dt, 1H, J = 9.92, 1.15 Hz, CH_2–CH=**CH_2**-*cis*), 2.90 (br.s, 2H, carborane CH), 1.80 (br.s, 2H, -CH_2-B^9). ^{11}B NMR (128.28 MHz, $CDCl_3$) δ (ppm): 0.22 (s, 1B, B^9), −6.54 (d, 2B, J = 161.3 Hz), −10.03 (d, 1B, J = 150.4 Hz) −13.24 (d, 2B, J = 163.5 Hz), −13.94 (d, 2B, J = 163.5 Hz), −17.59 (d, 1B, J = 180.3 Hz) −20.26 (d, 1B, J = 181.1 Hz). *Anal.* Calc. for $C_5H_{16}B_{10}$, (184.3): C, 32.59; H, 8.75; B, 58.66 Found: C, 32.72; H, 8.95; B, 58.33%.

2.2.2. 9-Allyl-o-carborane (*4*)

Yield: 6.0 g (96%). Colorless oil. B.p. 85–86 °C/1 mmHg [76]. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.78 (ddt, 1H, J = 16.87, 9.31, 7.95 Hz, =**CH**–CH_2–B^9), 4.80 (dt, 1H, J = 16.87, 1.25 Hz, CH_2–CH=**CH_2**-*trans*), 4.78 (d, 1H, J = 9.31 1.25 Hz, CH_2–CH=**CH_2**-*cis*), 3.55 (br.s, 1H, carborane CH), 3.48 (br.s, 1H, carborane CH), 1.65 (br.s, 2H, –CH_2–B^9). ^{11}B NMR (128.28 MHz, $CDCl_3$) δ (ppm): 7.80 (s, 1B, B^9), −2.05 (d, 1B, J = 146.6 Hz), −8.87 (d, 2B, J = 149.0 Hz), −13.80 (d, 2B, J = 159.5 Hz), −14.35 (d, 2B, J = 163.5 Hz), −16.34 (d, 2B, J = 185.6 Hz). *Anal.* Calc. for $C_5H_{16}B_{10}$, (184.3): C, 32.59; H, 8.75; B, 58.66 Found: C, 32.69; H, 8.90; B, 58.41%.

2.3. Preparation of 9,10-diallyl-m-carborane (*13*)

To a mixture of 9,10-diiodo-*m*-carborane (6.0 g, 15.2 mmol) and $(PPh_3)_2PdCl_2$ (71 mg, 0.1 mmol) in ether (35–50 mL) allyl magnesium bromide (75 mmol, 52 mL, 1.44 M solution) was added dropwise with extensive stirring in argon atmosphere. The resulting mixture was refluxed for 10 h until TLC (eluent $CHCl_3$) indicated complete disappearence of the diodocarborane. After the completion of the reaction hydrochloric acid (40 mL, 1.6 N) was added dropwise to the reaction mixture. Organic layer was separated and washed with water, sat. aq $Na_2S_2O_3$ solution (50 mL) and dried over $MgSO_4$. After removal of solvent, the crude product was purified by column chromatography on a silica gel with heptane as an eluent to afford corresponding diallyl carborane **13**. Yield: 3.24 g (95%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.88 (ddt, 2H, J = 17.01, 9.39, 7.63 Hz, =**CH**–CH_2–$B^{9,10}$), 4.88 (dt, 2H, J = 17.01, 1.07 Hz, CH_2–CH=**CH_2**-*trans*), 4.83 (dt, 2H, J = 9.38, 1.07 Hz, CH_2–CH=**CH_2**-*cis*), 2.82 (br.s, 2H, carborane CH), 1.76 (br.s, 4H, –CH_2–$B^{9,10}$). ^{11}B NMR (128.28 MHz, $CDCl_3$) δ (ppm): −0.42 (s, 2B, B^9, B^{10}), −6.50 (d, 2B, J = 158 Hz), −13.82 (d, 4B,