Tetrahedron 75 (2019) 1323–1325

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The first example of a "click" reaction with a carboranyl azide and an olefin

Uday B. Chauhan, Anton W. Tomich**, Vincent Lavallo*

Department of Chemistry, University of California, Riverside, 501 Big Springs Road, Riverside, CA 92521, United States

ARTICLE INFO

Article history:
Received 13 December 2018
Received in revised form
18 January 2019
Accepted 22 January 2019
Available online 24 January 2019

Keywords:
Carboranes
Click chemistry
Metal-free click
Heterocycles
Triazoline

ABSTRACT

While typical organic azides have long been known to undergo 1–3 dipolar cycloadditions with strained C–C multiple bonds, such chemistry has never been reported between organomimetic carboranyl azides and alkenes. Here we show that the carborane *o*-$PhCN_3CB_{10}H_{10}$ readily undergoes cycloaddition with norbornene at ambient temperature to afford the corresponding triazole adduct with perfect *exo*-selectivity. The structure of the ensuing heterocycle was unambiguously determined by multinuclear NMR, correlation NMR, and single crystal X-ray diffraction experiments. This first example of such reactivity demonstrates a method to easily introduce carborane clusters directly to scaffolds of interest, without having an organic spacer between the azide functionality and cluster.

1. Introduction

"Click" chemistry involves the 1–3 dipolar cycloaddition of an azide with a C–C multiple bond to form 5-membered ring heterocycles [1–6]. Most commonly a Cu catalyst is utilized to initiate such azide cycloadditions with alkynes. However, these reactions can occur without a catalyst if the C–C multiple bond is strained, as in cyclooctynes [3] and norbornenes [6,7]. Over the last several decades, such "click" reactions have become an exceedingly popular strategy to introduce triazole fragments into complex molecules for fine chemical [2] and materials synthesis [8,9]. Additionally, non-catalyzed "click" reactions with both strained alkenes and alkynes yielding 1,2,3-triazoles have found utility in bio-orthogonal chemistry as a method to assemble biomarkers in intracellular environments [6,7]. Through similar methods to the popular Staudinger ligation, click reactions that do not involve a cytotoxic copper metal catalyst have proven an elegant solution to the synthesis of fluorescent probes in biological media.

Carboranes [10–19] are an intriguing class of molecules that have found applications across a wide variety of fields due to their unique 3-D aromatic properties, steric profile, and chemical inertness [18,19]. Among these compounds, the electronically neutral 1,2-$C_2B_{10}H_{12}$, or *ortho*-carborane, has found applications in carborane-based ligand platforms [11] for catalysis and therapeutics [15]. (3) The reactivity of these 3-D aromatic systems often parallels that of 2-D phenyl substituents in terms of electrophilic aromatic substitution. Interestingly, while "click" reactions have been reported between azides/alkynes, featuring distant carborane groups [20–22], only a single report by Xie et al. has thus far surfaced of "click" chemistry between electronically distinct carboranyl azides and alkynes [23] (N atom of azides bound directly to the cage). For this reason, we sought to investigate the reactivity of an *o*-carboranyl azide with a strained alkene, which if successful, could allow for new synthetic routes to previously unknown carborane appended heterocycles. Recently, related carborane fused heterocycles have displayed interesting electronic properties [24–28].

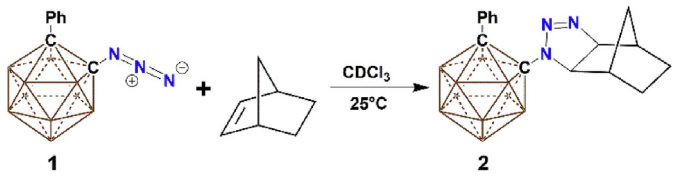
2. Results

While the parent *o*-carboranyl azide N_3-$CCHB_{10}H_{10}$ is volatile and relatively unstable [29], C-substituted derivatives N_3-$CCRB_{10}H_{10}$ are less volatile and only extrude N_2 at elevated temperatures. Hence, we targeted the reaction between the readily available phenyl substituted derivative **1** [33] and norbornene (Scheme 1).

Reaction of **1** with norbornene was performed in deuterated chloroform in which immediate formation of a single isomer of a

* Corresponding author.
** Corresponding author.
E-mail address: vincentl@ucr.edu (V. Lavallo).

https://doi.org/10.1016/j.tet.2019.01.049
0040-4020/



Scheme 1. Reaction of **1** with norbornene to yield carboranyl azide adduct **2**.

new compound **2** was observed via multinuclear NMR (Scheme 1). The $^{11}B[^{1}H]$ NMR spectra of the new compound **2** displays two distinct resonances (−3.67 and −5.21 ppms) for the unique borons antipodal to the carbon atoms of the cluster, as well as a group of overlapping signals between −7.54 and −18.00 ppms for the remaining 8 boron vertices in the cluster (Fig. S1). The ^{13}C NMR of the same compound reveals 12 unique resonances along with the disappearance of the olefin signal associated with the norbornene starting material (Fig. S2). A ^{13}C DEPT 135 experiment confirmed that there were three CH_2 resonances in the norbornene ring system (Fig. S3).

More compelling evidence for the predicted carboranyl adduct **2** can be gleaned from the ^{1}H NMR, which reveals a desymmetrization of the norbornene molecule through emergence of a number of ^{1}H NMR resonances. Perhaps the most telling characteristic of successful carboranyl triazoline formation is the difference in chemical shifts between the alkene protons of the norbornene starting material and those of the suspected heterocycle. Indeed, the resulting ^{1}H NMR displays two doublets, which emerge at 3.94 and 2.83 ppms, suggesting close proximity to the electronegative N atoms (Fig. S4). Further analysis of the ^{1}H NMR spectra corroborates these suspicions as the bridgehead methylene protons H_e/H_f appear as two doublets at 0.43 and 0.22 ppms ($^{2}J = 11$ Hz), respectively. The broad bump located from 2.0 to 4.0 ppm in the ^{1}H NMR corresponds to the carboranyl B-H vertices (Fig. S4). A COSY NMR experiment corroborates the assignment of H_a-H_d, and confirms protons H_a and H_b engage in a ^{3}J coupling as evident by a cross peak at 3.94, 2.83 ppm (Fig. S5). No spin-spin coupling was observed between H_a/H_b and the adjacent methine protons, H_c/H_d (Fig. 1). The COSY also reveals H_c and H_d do not engage in ^{3}J couplings to any adjacent protons. Furthermore, the COSY confirms the diastereotopic methylene protons, H_g-H_j, couple with each other as evidenced by a cross-peak at 0.71, 1.08 ppm (Fig. S5). The aromatic region of the ^{1}H NMR spectra displays three characteristic resonances corresponding to the phenyl substituent of **1**, which is further corroborated by cross peaks in the aromatic region of the COSY.

The structure of **2** was unambiguously determined by a single crystal x-ray diffraction study to be the *exo*-isomer of the cycloaddition reaction (Fig. 2). The triazoline heterocycle is perfectly planar as revealed by the sum of the internal bond angles totaling 540°. The N_2–N_3 bond length (1.2435(11) Å) is significantly shorter

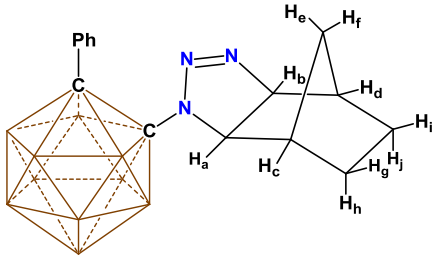


Fig. 1. Proton assignment of carboranyl azide adduct **2**.

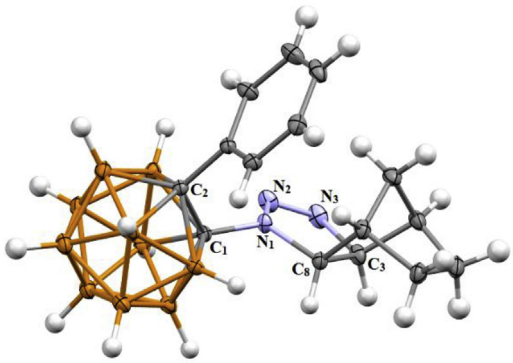


Fig. 2. Solid-state crystal structure of compound **2** displaying C (gray), B (orange), N (blue), and H (white) atoms.

than that of the $N_1 - N_2$ bond (1.4097(10) Å), indicating greater multiple bond character between N_2 and N_3. Interestingly, the C_1–N_1 bond appending the carborane to the heterocycle has a noticeably shorter bond length of 1.4008(10) Å in comparison to the C–N bonds present on the triazoline ($C_8 - N_1 = 1.4750$ Å, C_3–$N_3 = 1.4829$ Å). In addition, the C_1–N_1 bond length of **2** is shortened with respect to the starting azide (1.4282(13)) **1** [30]. Comparable C– N bond lengths have been reported for 1-amino-2-Ph-*o*-carborane (mean 1.392(3) Å) and suggest some degree of *exo*-π-conjugation between the cluster and heterocycle [31]. A few *o*-carboranyl amine derivatives reported by Xie et al. have also been shown to possess a similar C–N bond distance [32]. This is complemented by dramatic lengthening of the *o*-carborane C–C bond on the same compound (mean 1.836 Å). Indeed, the short C_1–N_1 bond length observed in **2** is corroborated by the 2-Ph-*o*-carborane moiety C_1–C_2 distance of 1.7735 Å, significantly longer than the C_1–C_2 bond in azide **1** (1.725(5) Å) [33]. Overall, this suggests the triazoline N_1 acts as a π-donor when bonded directly to the 2-Ph-*o*-carborane moiety, although less conjugation is observed compared to *o*-carboranyl amine derivatives.

3. Conclusion

As demonstrated above carboranyl azides are viable reaction partners for the "click" chemistry with strained C–C multiple bonds. This discovery paves the way for the elaboration of this methodology to different carboranyl azides and strained alkenes/alkynes. Such a strategy should allow facile access to heterocycles appended with *o*-carborane substituents, which are not easily obtained any other way. These species will likely find applications as pharmaceutical and functional material precursors. We are currently exploring the viability of using other carboranyl azides, such as those derived from *closo*-carborane anions.

4. Experimental

4.1. General considerations

Unless otherwise stated, all manipulations were carried out using standard Schlenk or glovebox techniques (O_2, $H_2O < 1$ ppm) under a dinitrogen or argon atmosphere. Solvents were dried over K or CaH_2, and distilled under argon before use. Reagents were purchased from commercial vendors and used without further purification. NMR spectra were recorded on Bruker Avance 300 MHz or Varian Inova 300–500 MHz spectrometers. Standard Varian pulse sequence gCOSY was used for the COSY experiment. NMR chemical shifts are reported in parts per million (ppm). ^{1}H

NMR and ^{13}C NMR chemical shifts were referenced to residual non-deutero solvent. ^{11}B NMR chemical shifts were externally referenced to $BF_3 \cdot OEt_2$. Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR Spectrometer.

4.1.1. Synthesis of carboranyl azide adduct, ***2***

1-N_3-2-Ph-$C_2B_{10}H_{10}$, 1, was prepared following a synthesis published by Kennedy [33]. **1** (52.27 mg, 0.20 mmol), and Bicyclo [2.2.1]hept-2-ene (18.83 mg, 0.20 mmol), were dissolved in Chloroform-d (2.00 mL, 24.9 mmol) in a 20 mL glass scintillation vial and stirred at room temperature for 7 h. The solvent was evaporated to obtain 69.10 mg of product as a white solid and recrystallized from slow evaporation of toluene (0.19 mmol, 97.1%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 7.58$ (d, 2H, CH_{aryl}, $^3J(H-H) = 7.8$ Hz), 7.11 (t, ^1H, CH_{aryl}, $^3J(H-H) = 7.5$ Hz), 7.00 (dd, 2H, CH_{aryl}, $^3J(H-H) = 7.7$ Hz, $^3J(H-H) = 8.7$ Hz), 3.96 (d, ^1H, CH, $^3J(H-H) = 8.7$ Hz), 2.10–3.57 (br, 10H, BH), 2.83 (d, 2H, CH, $^3J(H-H) = 8.7$ Hz), 2.31 (s, 1H, CH), 1.54 (s, 1H, CH), 1.08 (m, 2H, CH_2), 0.71 (m, 2H, CH_2), 0.42 (d, 1H, CH, $^2J(H-H) = 11$ Hz), 0.21 (d, 1H, CH, $^2J(H-H) = 11$ Hz) ppm. ^{13}C NMR (126 MHz, Toluene-d_8) $\delta = 131.7$, 130.9, 130.5, 128.6, 96.3, 90.5, 88.2, 62.7, 45.2, 42.4, 40.4, 36.4, 31.4, 25.5, 24.2 ppm. ^{11}B NMR (160 MHz, Toluene-d_8) $\delta = -3.7$, −5.2, 10.1, −11.9 ppm. M.P.: 120–122 °C.

Acknowledgments

We are grateful to the National Science Foundation of the USA for funding this work (Grants CHE-1455348; MRI-1626673).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.01.049.

References

[1] M.S. Singh, S. Chowdhury, S. Koley, Tetrahedron 72 (2016) 5257.
[2] J.E. Moses, A.D. Moorhouse, Chem. Soc. Rev. 36 (2007) 1249.
[3] E.M. Sletten, C.R. Bertozzi, Acc. Chem. Res. 44 (2011) 666.
[4] V.K. Tiwari, B.B. Mishra, K.B. Mishra, N. Mishra, A.S. Singh, X. Chen, Chem. Rev. 116 (2016) 3086.
[5] P. Thirumurugan, D. Matosiuk, K. Jozwiak, Chem. Rev. 113 (2013) 4905.
[6] E.M. Sletten, C.R. Bertozzi, Angew. Chem. Int. Ed. 48 (2009) 6974.
[7] T. Sasaki, S. Eguchi, M. Yamaguchi, T. Esaki, J. Org. Chem. 46 (1981) 1800.
[8] A. Qin, J.W.Y. Lam, B.Z. Tang, Chem. Soc. Rev. 39 (2010) 2522.
[9] D.A. Fleming, C.J. Thode, M.E. Williams, Chem. Mater. 18 (2006) 2327.
[10] A.M. Spokoyny, Pure Appl. Chem. 85 (2013) 903.
[11] A.R. Popescu, F. Teixidor, C. Viñas, Coord. Chem. Rev. 269 (2014) 54.
[12] J. Zhang, Z. Xie, Acc. Chem. Res. 47 (2014) 1623.
[13] Z. Qiu, S. Ren, Z. Xie, Acc. Chem. Res. 44 (2011) 299.
[14] B.J. Eleazer, D.V. Peryshkov, Comments Inorg. Chem. 1 (2018).
[15] M. Scholz, E. Hey-Hawkins, Chem. Rev. 111 (2011) 7035.
[16] R.N. Grimes, Dalton Trans. 44 (2015) 5939.
[17] N.S. Hosmane, R. Eagling, Handbook of Boron Science: with Applications in Organometallics, Catalysis, Materials and Medicine, 2018.
[18] N.S. Hosmane, Boron Science : New Technologies and Applications, CRC Press, Boca Raton, 2016.
[19] R.N. Grimes, Carboranes, Elsevier, Amsterdam, 2016.
[20] R. Djeda, J. Ruiz, D. Astruc, R. Satapathy, B.P. Dash, N.S. Hosmane, Inorg. Chem. 49 (2010) 10702.
[21] B.P. Dash, R. Satapathy, B.P. Bode, C.T. Reidl, J.W. Sawicki, A.J. Mason, J.A. Maguire, N.S. Hosmane, Organometallics 31 (2012) 2931.
[22] V.A. Ol'shevskaya, A.V. Makarenkov, Y.A. Borisov, I.V. Ananyev, E.G. Kononova, V.N. Kalinin, A.B. Ponomaryov, Polyhedron 141 (2018) 181.
[23] R. Cheng, Z. Qiu, Z. Xie, Nat. Commun. 8 (2017) 14827.
[24] J.H. Wright, C.E. Kefalidis, F.S. Tham, L. Maron, V. Lavallo, Inorg. Chem. 52 (2013) 6223.
[25] A.L. Chan, J. Fajardo, J.H. Wright, M. Asay, V. Lavallo, Inorg. Chem. 52 (2013) 12308.
[26] M. Asay, C.E. Kefalidis, J. Estrada, D.S. Weinberger, J. Wright, C.E. Moore, A.L. Rheingold, L. Maron, V. Lavallo, Angew. Chem. Int. Ed. 52 (2013) 11560.
[27] T.L. Chan, Z. Xie, Chem. Sci. 9 (2018) 2284.
[28] C.-X. Cui, S. Ren, Z. Qiu, Z. Xie, Dalton Trans. 47 (2018) 2453.
[29] R.J. Blanch, L.C. Bush, M. Jones, Inorg. Chem. 33 (1994) 198.
[30] J. Fajardo, A.L. Chan, F.S. Tham, V. Lavallo, Inorg. Chim. Acta. 422 (2014) 206.
[31] L.A. Boyd, W. Clegg, R.C.B. Copley, M.G. Davidson, M.A. Fox, T.G. Hibbert, J.A.K. Howard, A. Mackinnon, R.J. Peace, K. Wade, Dalton Trans. (2004) 2786.
[32] R. Cheng, J. Zhang, J. Zhang, Z. Qiu, Z. Xie, Angew. Chem. Int. Ed. 55 (2016) 1751.
[33] R.D. Kennedy, Chem. Commun. 46 (2010) 4782.