Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Accessing the Rare Diazacyclobutene Motif

Chandima J. Narangoda,[†] Timothy R. Lex,[†] Madelyn A. Moore,[†] Colin D. McMillen,[†] Alex Kitaygorodskiy,[†] James E. Jackson,[‡] and Daniel C. Whitehead*[,†,§]

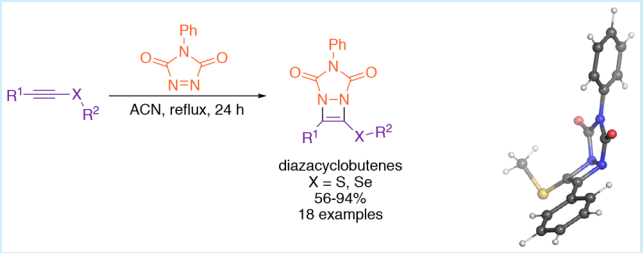
[†]Department of Chemistry, Clemson University, Clemson, South Carolina 29634, United States

[‡]Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States

[§]Eukaryotic Pathogens Innovation Center, Clemson University, Clemson, South Carolina 29634, United States

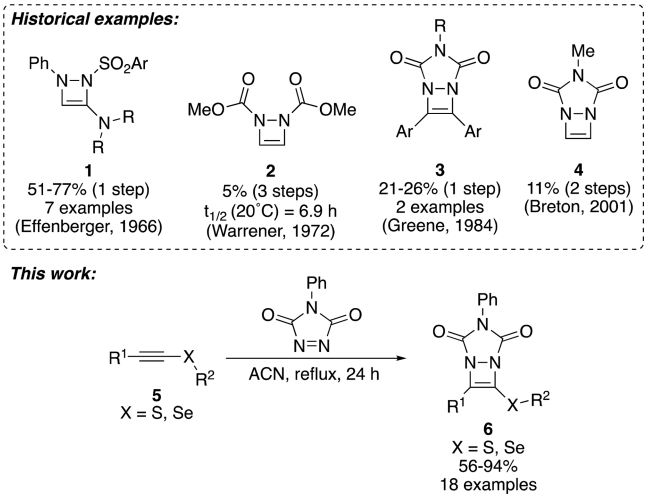
Supporting Information

ABSTRACT: A formal [2 + 2] cycloaddition of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) with electron-rich alkynyl sulfides and selenides is described. These investigations provide a convenient method to access diazacyclobutenes in good yield while tolerating a relatively broad substrate scope of thio-acetylenes. This method provides ready access to a unique and hitherto rarely accessible class of heterocycles. A combination of dynamic NMR, X-ray crystallography, and computation sheds light on the potential aromaticity of the scaffold.



The triazolinediones, such as 4-phenyl- and 4-methyl-1,2,4-triazoline-3,5-dione (PTAD and MTAD, respectively) have proven to be versatile synthetic tools to effect a number of useful transformations.[1] We present here the results of a study that evaluated the reactivity of these species with electron-rich alkynyl sulfides and selenides for the preparation of a rarely accessible molecular architecture, the diazacyclobutenes.[2] The diazacyclobutenes (**1**−**4**, **6**) are a unique class of four membered heterocycles consisting of a carbon−carbon double bond and two adjacent nitrogen atoms (Scheme 1). Historically, these heterocycles gained attention in the literature owing to the electronic framework resident in the moiety that formally follows the Hückel (4*n*+2) rule of aromaticity.[3,4] Thus, these molecules, their potential aromaticity, and their putative reactivity have been the subject of several computational[5−9] and comparatively fewer synthetic studies.[5,10−13] Despite the first report on the preparation of a small set of stable diazacyclobutenes appearing over half a century ago,[10] less than 10 examples of this scaffold are known (**1**−**4**), and typically have been accessed in rather poor yields.[5,10−13]

Scheme 1. Historical Examples of Diazacyclobutenes and a New Synthetic Route

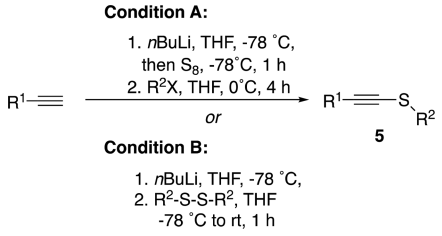


With an interest in accessing this interesting and relatively unexplored scaffold, we set out to develop a convenient method to synthesize diazacyclobutenes. Initial grounding experiments focused on combining PTAD and unmodified alkynes (i.e., similar to the work of Greene)[12] under a variety of conditions, efforts that ultimately failed to bear any productive fruit. We next hypothesized that more electron-rich alkynes might fare better in the desired transformation. Thus, we settled on the preparation of a series of alkynyl sulfides, which provided enhanced electron density on the alkyne substrate coupled with relative ease of synthesis (Scheme 2). Briefly, the alkynyl sulfides, **5**, were accessible by direct deprotonation of terminal alkynes followed by either interception with elemental sulfur followed by quenching the incipient sulfide anion with an alkyl halide (Condition A), or direct reaction of the lithium acetylide intermediate with an appropriate dialkyl disulfide (Condition B) (see Supporting Information (SI) for more details).[14−16] Two alkynyl selenides were also prepared using analogous conditions to those depicted in Scheme 2.[17,18]

Received: November 9, 2018

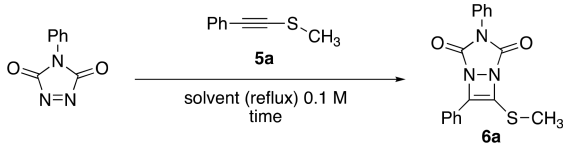
DOI: 10.1021/acs.orglett.8b03590
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Synthesis of Alkynyl Sulfides



Next, we investigated the potential cycloaddition between PTAD and methyl phenylethynyl sulfide (i.e., **5a**) to provide the corresponding diazacyclobutene **6a** (Table 1). We first examined the yield of the reaction when PTAD (1 equiv) and **5a** (1.3 equiv) were heated under reflux conditions for 24 h in a series of common solvents (entries 1−5). Acetonitrile was found to afford the highest yield (i.e 89% yield, entry 5) of diazacyclobutene **6a**, although the transformation tolerates a range of solvents reasonably well. Chloroform and dichloromethane gave slightly lower yields of 82% and 78%, respectively, whereas tetrahydrofuran and toluene provided even lower yields of 68% and 67% (entries 1−4). Reaction conditions were further tuned by conducting a time study: refluxing in acetonitrile for 6 h (80%) and 12 h (83%) returned **6a** in good but slightly lower yields compared to the corresponding 24 h reaction (entries 6−7). Furthermore, decreasing the equivalence of alkynyl sulfide **5a** resulted in lower isolated yields of product **6a** (i.e., 71%, 69%, and 72% yield for 1.0, 1.1, and 1.2 equiv **5a**, respectively (entries 8−10)). Finally, when the concentration of the reaction was doubled (i.e., to 0.2 M in PTAD), the yield was also diminished to 75% of **6a** (entry 11). Thus, on the basis of these observations we selected the conditions in entry 5 (highlighted in bold) as the optimal conditions. The cyclization of related *N*-methyl-*N*-tosyl ynamines and silyl ynol ethers proceeded rather poorly under the present reaction conditions (i.e., 30−40% yield for ynamines in the presence of a Lewis acid catalyst, and not at all with silyl ynol ethers). The continued optimization of these substrate classes remains an area of active study in our laboratory.

Table 1. Optimization of Diazacyclobutene synthesis

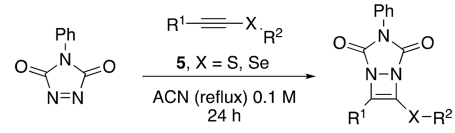


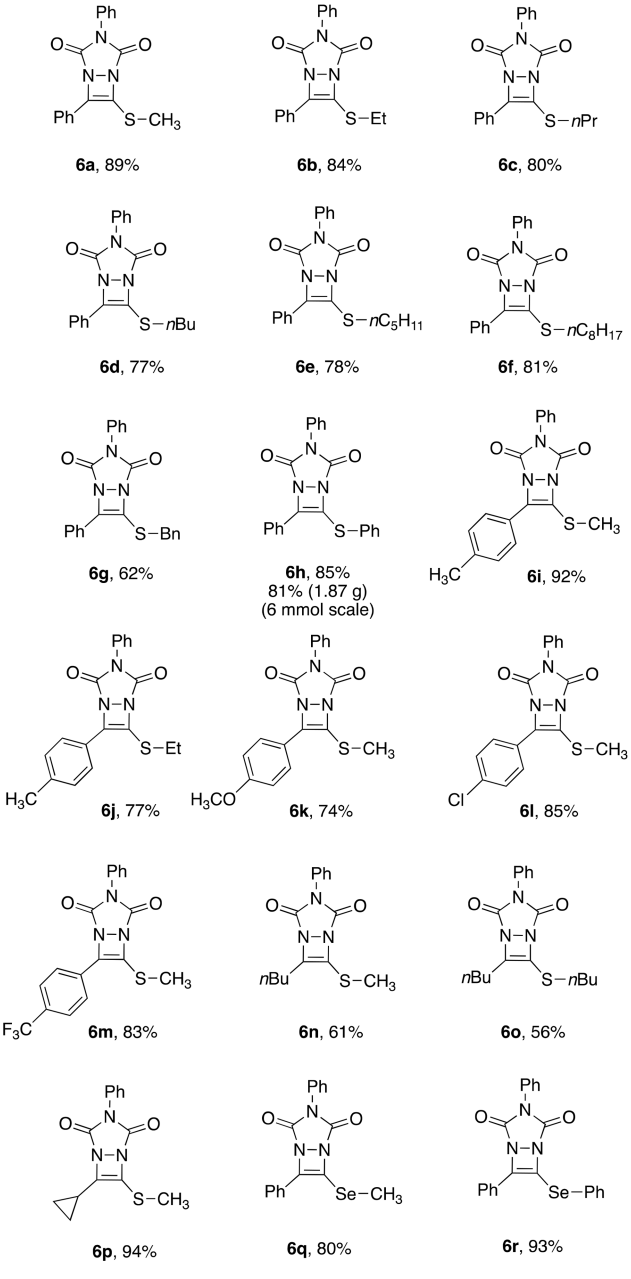
entry	solvent	**5a** (equiv)	time [h]	yield [%][a]
1	$CHCl_3$	1.3	24	82
2	DCM	1.3	24	78
3	THF	1.3	24	68
4	toluene	1.3	24	67
5	**ACN**	**1.3**	**24**	**89**
6	ACN	1.3	6	80
7	ACN	1.3	12	83
8	ACN	1.0	24	71
9	ACN	1.1	24	69
10	ACN	1.2	24	72
11[b]	ACN	1.3	24	75

[a]Isolated yields after column chromatography. [b]Reaction conducted at 0.2 M. DCM = dichloromethane, THF = tetrahydrofuran, ACN = acetonitrile.

We next explored the substrate scope of the transformation (Scheme 3). First, we evaluated varying the length of the alkyl chain resident on the sulfur atom (i.e., R^2) of the alkynyl sulfide component (**6a**−**6f**). Products bearing shorter *n*-alkyl chains at R^2 such as methyl, ethyl, *n*-propyl, and *n*-butyl were successfully converted into their corresponding diazacyclobutene derivatives **6a**−**d** in 77−89% yields. The diazacyclobutene derivatives **6e** and **6f** bearing *n*-pentyl and *n*-octyl groups at

Scheme 3. Substrate Scope (1 mmol Scale)





DOI: 10.1021/acs.orglett.8b03590
Org. Lett. XXXX, XXX, XXX−XXX

sulfur were generated in 78% and 81% yields, respectively. Incorporating a benzyl group at R^2 returned **6g** in moderate yield (62%), while the R^2 = Ph analogue (**6h**) was prepared in 85% isolated yield at 1 mmol scale.

We then examined the reactivity of alkyl phenylacetylene sulfides bearing *para*-substituted electron donating and withdrawing substituents on the phenyl group situated at R^1. Substrates with arenes bearing electron donating groups such as *p*-methyl (i.e., **6i** and **6j**, 92 and 77% yields, respectively) and *p*-methoxy (i.e., **6k**, 74% yield) proceeded in good yield. Substrates with arenes bearing electron withdrawing substituents such as *p*-chloro and *p*-trifluoromethyl (**6l**–**m**, 85 and 83%, respectively) also generated the corresponding diazacyclobutene derivatives in good yields. We also probed the transformation with thio-acetylenes bearing an alkyl chain (i.e. *n*-butyl) at R^1 in lieu of an arene. Thus, diazacyclobutenes **6n** (R^2 = methyl) and **6o** (R^2 = *n*-butyl) were prepared in moderate yields of 61% and 56%, respectively. Additionally, diazacyclobutene **6p**, for which R^1 = cyclopropyl, was prepared in 94% yield. Finally, modulating the chalcogen in the system to selenium provided two examples, **6q** and **6r**, in 80 and 93% yield, respectively. The reaction also scales reasonably well. The synthesis of **6h** was carried out on a 6 mmol scale, returning the diazacyclobutene in 81% isolated yield (1.87 g).

The compounds presented in Scheme 3 are almost universally crystalline. Thus, we have obtained single crystal X-ray structures of 11 of them (see Figure 1 for **6k**; see SI for more details and data for **6a**–**c**, **6h**, **6i**, **6l**, **6m**, **6p**, **6q**, and **6r**; CCDC 1871105–1871115 contain the supplementary crystallographic data for this manuscript). Leveraging this data and our ability to access a large number of diazacyclobutene derivatives for the first time, we were in a position to evaluate the potential aromaticity of this class of molecules by exploring the X-ray structures of the diazacyclobutene core in a suite of electronically distinct compounds (see section VI in SI). Indeed, the core diazacyclobutene scaffold formally obeys the Hückel 4*n*+2 rule for aromaticity, and a number of computational studies have explored the potential for aromaticity in this system.[5−7,9] However, all of the compounds that we have analyzed by X-ray crystallography show a puckered structure with the five-membered ring canted out-of-plane with respect to the core diazacyclobutene moiety. On average, the angle of intersection of the four-membered and five-membered ring planes is θ = 125.0 ± 1.8°, see Figure 1A and Table S4).

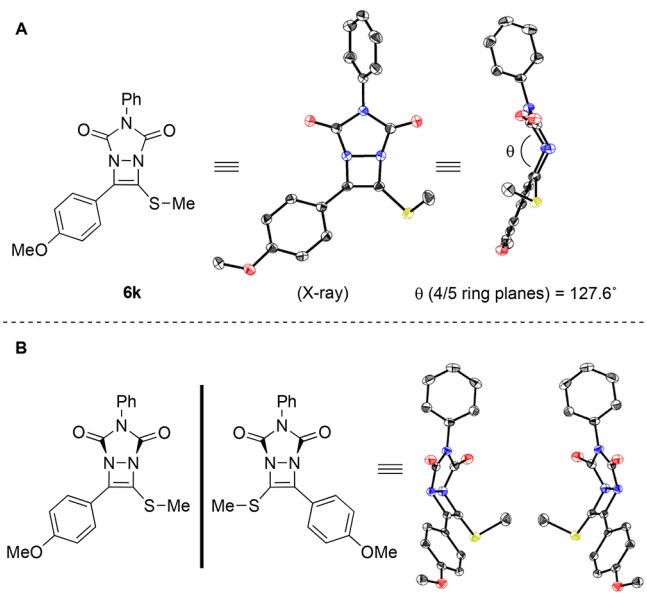


Figure 1. (A) Single crystal X-ray structure of diazacyclobutene **6k**, highlighting the 4/5 ring plane intersection angle, θ. (B) Enantiomers evident in the X-ray structure.

The puckered geometry of the 4/5 bicyclic ring system results in the appearance of two distinct enantiomers (Figure 1B) in the unit cell for every compound we have probed by X-ray analysis. These two enantiomers appear to rapidly equilibrate at room temperature. Thus, we analyzed the double nitrogen inversion barrier by means of dynamic ^{1}H NMR analysis[19] under cryogenic conditions. Specifically, the S-benzyl methylene protons in diazacyclobutene **6g** appear as a clean singlet (4.21 ppm, 300 MHz) at room temperature, but gradual cooling of the sample to −25 °C revealed a clear coalescence point followed by resolution into a clean AB quartet (4.22 ppm, 4.15 ppm, J = 12.8 Hz), indicative of diastereotopicity at lower temperatures (see Figure 2A for experimental spectra). Dynamic NMR simulations and line shape analyses were performed using Bruker Topspin version 3.5 software, and the exchange rate constant, K_{ex}, was extracted. An Eyring plot (Figure 2B) was used to calculate the $\Delta H^{‡}$ and $\Delta S^{‡}$ terms: 14.4 ± 0.7 kcal/mol and 3.2 ± 2.7 cal/mol·K, respectively. From these data, the activation energy, ($\Delta G^{‡}$), for the inversion was determined to be 13.4 ± 0.7 kcal/mol at 298 K (25 °C). A similar analysis was conducted for the S-ethyl methylene protons in **6b** (see SI), revealing an inversion barrier, $\Delta G^{‡}$, of 13.6 ± 0.5 kcal/mol at 298 K (25 °C).

Finally, we evaluated the inversion barrier computationally for **6a** at 25 °C in the gas phase and in simulated chloroform solvent, using the wB97X-D/6-311+G(2df,2pd) DFT method[20] and the SMD solvation model of Cramer et al.[21] as implemented in the Gaussian 16 program suite.[22] The results, $\Delta H^{‡}$ = 12.6 and 11.3 kcal/mol respectively, show solvation lowering the enthalpy barrier to inversion. This finding surprised us, but accords with the larger dipole moment (2.62 vs 2.25 D) calculated for the near-planar transition structure (TS) for inversion than for the strongly bent ground state (GS) minima. To further explore this issue, we reanalyzed the above TS and GS structures using the wave function-based T1 method of Hehre et al.,[23] with solvation computed at the B3LYP/6-31+G*/SM8 level, as implemented in the Spartan quantum chemistry code (Figure 3).[24] The resulting gas- and $CHCl_3$ solvated barriers were 14.9 and 14.2 kcal/mol, respectively, in good agreement with experiment. Inclusion of entropy terms to compute free energy barriers did not change them from the above values, consistent with the small $\Delta S^{‡}$ values obtained experimentally.

The increase and orientation of the dipole in the flat inversion TS suggest that charge may be shifting from the vicinal nitrogen centers into the carbonyl groups of the urazole ring, and perhaps gaining some delocalization and potentially aromatic stabilization for these two formally 4*n*+2 π electron rings. To probe this question, we performed NICS(1)zz (Nucleus Independent Chemical Shift) calculations on all four rings of the GS and TS structures. NICS(1)zz extracts the out-of-plane (zz) tensor component of the isotropic NICS, thus minimizing σ-orbital contributions.[25] Positive values of ΔNICS(1)zz upon ring flattening would indicate increased paratropic (i.e., antiaromatic) ring current, suggesting destabi-

DOI: 10.1021/acs.orglett.8b03590
Org. Lett. XXXX, XXX, XXX−XXX

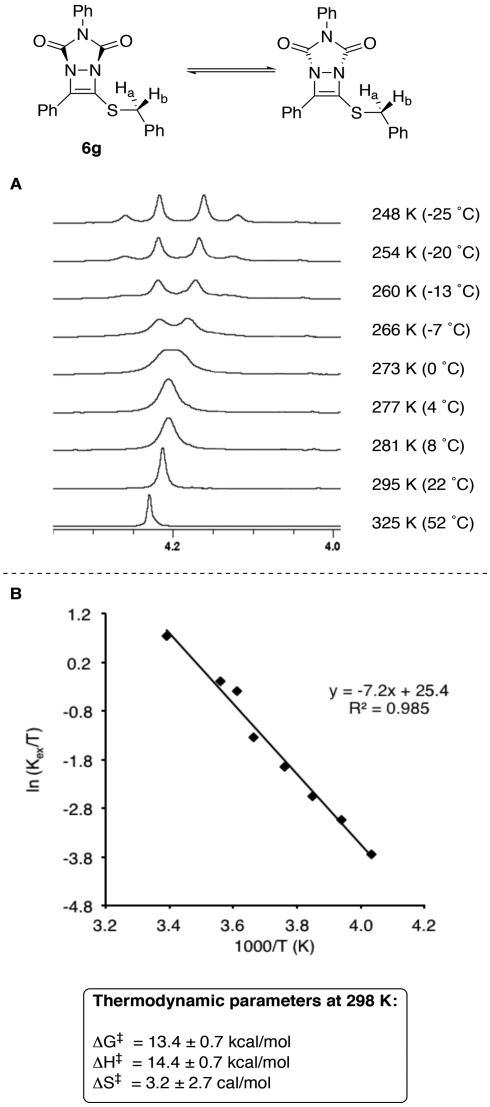


Figure 2. Dynamic NMR analysis (300 MHz) of the inversion barrier of **6g**. (A) Experimental spectra at variable temperature. (B) Eyring plot originating from simulated spectra. Box: Thermodynamic parameters for the inversion barrier extracted from the Eyring plot.

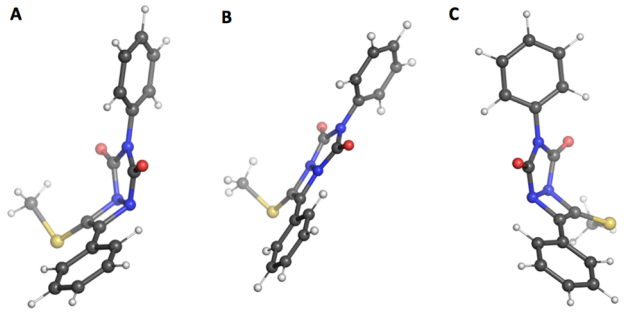


Figure 3. Calculated minima (**A** and **C**) and transition state (**B**) for the double nitrogen inversion of **6a** calculated at the wB97X-D/6-311+G(2df,2pd) level.

lization of the TS, and vice versa. The ΔNICS(1)zz values observed for both the four- and five-membered rings show substantial paratropic shifts at −3.2 and −4.8 ppm for probe sites positioned 1 Å above the center of the respective rings (exo face, for GS). The implication is that despite improved π overlap and potential for delocalization, aromaticity is not an element in stabilizing the inversion TS.

On the basis of the puckered nature of the scaffold that is evident in every example that we have analyzed by X-ray crystallography, and on the basis of the experimental observation of the racemizing inversion by dynamic ^{1}H NMR, and our computational results, it appears that the diazacyclobutanes arising from our study are not aromatic, even in the TS that is traversed during the inversion process. Our observations provide experimental evidence that corroborates the conclusions drawn earlier computationally by others.[5−7,9]. For a broader historical perspective on the potential aromaticity of diazacyclobutenes, see section VI in the SI.

In conclusion, we have developed a straightforward approach for the synthesis of rare diazacyclobutanes by means of a formal [2 + 2] cycloaddition between alkynyl sulfides or selenides and PTAD. This effort provides ready access to a molecular scaffold that was hitherto inaccessible over the last half-century, with the exception of a handful of examples. Experimental and computational evidence suggests that the compounds are not aromatic, despite formally obeying the Hückel 4*n*+2 rule for aromaticity. Efforts are underway currently to expand the substrate scope of this transformation by exploring new triazoline diones and electron-rich alkynes, to probe the mechanism of the transformation, and to explore the further synthetic manipulation and biological activity of this unique molecular scaffold. More broadly, this study contributes to the challenging research area devoted to the preparation of four-membered and other strained heterocycles.[26,27]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03590.

Experimental details, further discussion on the potential aromaticity of diazacyclobutenes, X-ray crystallography data, and full characterization data for all synthetic compounds (PDF)

Accession Codes

CCDC 1871105−1871115 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*dwhiteh@clemson.edu

ORCID

Daniel C. Whitehead: 0000-0001-6881-2628

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Xinliang Ding (Michigan State University) for HRMS analyses.

DOI: 10.1021/acs.orglett.8b03590
Org. Lett. XXXX, XXX, XXX−XXX

REFERENCES

(1) De Bruycker, K.; Billiet, S.; Houck, H. A.; Chattopadhyay, S.; Winne, J. M.; Du Prez, F. E. *Chem. Rev.* **2016**, *116*, 3919−3974.

(2) A note on nomenclature: The core four-membered ring system in this scaffold has been previously referred to as a diazacyclobutene (which we adopt here), a Δ^3-1,2-diazetine, and a 1,2-dihydrodiazete (in compliance with IUPAC nomenclature guidelines). We adopt "diazacyclobutene" herein because we view that moniker to be more clearly intuitive to the organic chemist. Further, referring to the compounds as substituted 1,2-dihydrodiazetes elicits possible confusion since *N*-substituted variants, including all of the examples presented in this manuscript, necessarily lack hydrogen atoms on the nitrogen atoms within the core ring system despite their implied presence from the name.

(3) Richter, R.; Ulrich, H. The Chemistry of Heterocycles. *Small Ring Heterocycles, part 2*; Hassner, A., Ed.; Wiley: New York, 1983; Vol. *42*, pp 443−545.

(4) Vol'pin, M. E. *Russ. Chem. Rev.* **1960**, *29*, 129−160.

(5) Warrener, R. N.; Nunn, E. E.; Paddon-Row, M. N. *Aust. J. Chem.* **1979**, *32*, 2659−2674.

(6) Budzelaar, P. H. M.; Cremer, D.; Wallasch, M.; Würthwein, E.-U.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 6290−6299.

(7) Mó, O.; Yáñez, M.; Elguero, J. *J. Mol. Struct.: THEOCHEM* **1989**, *201*, 17−37.

(8) Bachrach, S. M.; Liu, M. *J. Org. Chem.* **1992**, *57*, 2040−2047.

(9) Breton, G. W.; Martin, K. L. *J. Org. Chem.* **2002**, *67*, 6699−6704.

(10) Effenberger, F.; Maier, R. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 416−417.

(11) Nunn, E. E.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1972**, 818−819.

(12) Cheng, C.-C.; Greene, F. D.; Blount, J. F. *J. Org. Chem.* **1984**, *49*, 2917−2922.

(13) Breton, G. W.; Shugart, J. H.; Hughey, C. A.; Perala, S. M.; Hicks, A. D. *Org. Lett.* **2001**, *3*, 3185−3187.

(14) Zheng, W.; Zheng, F.; Hong, Y.; Hu, L. *Heteroat. Chem.* **2012**, *23*, 105−110.

(15) Xie, L. G.; Niyomchon, S.; Mota, A. J.; González, L.; Maulide, N. *Nat. Commun.* **2016**, *7*, 10914.

(16) Gray, V. J.; Wilden, J. D. *Org. Biomol. Chem.* **2016**, *14*, 9695−9711.

(17) Alcaide, B.; Almendros, P.; Lázaro-Milla, C. *Adv. Synth. Catal.* **2017**, *359*, 2630−2639.

(18) Lang, H.; Keller, H.; Imhof, W.; Martin, S. *Chem. Ber.* **1990**, *123*, 417−422.

(19) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London; New York, 1982.

(20) Chai, J.-D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615−6620.

(21) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.

(22) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*, revision B.01; Gaussian, Inc.: Wallingford CT, 2016.

(23) Ohlinger, W. S.; Klunzinger, P. E.; Deppmeier, B. J.; Hehre, W. J. *J. Phys. Chem. A* **2009**, *113*, 2165−2175.

(24) *Spartan'16*; Wavefunction, Inc.: Irvine, CA.

(25) Schleyer, P. v. R.; Manoharan, M.; Wang, Z.-X.; Kiran, B.; Jiao, H.; Puchta, R.; van Eikema Hommes, N. J. R. *Org. Lett.* **2001**, *3*, 2465−2468.

(26) Anaya, J.; Sànchez, R. M. Four-Membered Ring Systems. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Amsterdam, 2018; Vol *30*, pp 77−108. See also, previous volumes.

(27) For a special issue of review articles on small heterocycles see: Andrei, Y. *Chem. Rev.* **2014**, *114* (16), 7783−8360.

DOI: 10.1021/acs.orglett.8b03590
Org. Lett. XXXX, XXX, XXX−XXX