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A Singlet Aryl-CF_3 Carbene: 2-Benzothienyl(trifluoromethyl)carbene and Interconversion with a Strained Cyclic Allene

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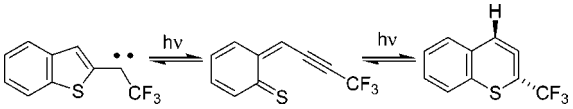
ABSTRACT



Matrix-isolated 2-benzothienyl(trifluoromethyl)carbene was generated by irradiation of the corresponding diazirine, and characterized by IR and UV/vis spectroscopy, in situ trapping, and DFT modeling. Experiments and calculations indicate that the carbene is a ground-state singlet, in contrast to previously characterized aryl(trifluoromethyl)carbenes. The carbene could be interconverted photochemically with a ring-opened thioquinomethide and a highly strained cyclic allene.

Aryl(trifluoromethyl)carbenes are among the most widely utilized reactive intermediates in photoaffinity labeling of biological systems.[1,2] Their precursors, trifluoromethyldiazirines, are relatively straightforward to prepare, are chemically stable under physiological conditions, can be attached to a variety of biologically relevant moieties, and undergo efficient photocleavage at convenient wavelengths. Despite the broad application of aryl-CF_3 carbenes, only a handful of studies have probed their chemistry, reactivity, and electronic structures.[3]

A question of mechanistic and practical relevance is the ground state multiplicity of these species. The ability to insert into, for example, R−H bonds concertedly may make singlet carbenes more effective in photoaffinity labeling than triplets in their ability to selectively attach to nearby biomolecules. Moreover, competing facile reaction with O_2 may lead to less efficient labeling by triplet carbenes. EPR, IR, and UV/vis spectroscopy indicates that phenyl-[4] and *p*-tolyl-(trifluoromethyl)carbenes[3a] are ground state triplets; similar information on other aryl-CF_3 carbenes, however, is sparce. We now report evidence for the first example of a singlet ground state aryl-CF_3 carbene, 2-benzothienyl(trifluoromethyl)carbene (**2**).

The 2-benzothienyl diazirine **1** was synthesized from the corresponding trifluoromethylketone[5] following standard procedures. Irradiation of **1** in a N_2 matrix at 10 K with 404 nm light converted it cleanly to carbene **2** (Scheme 1).[6] The carbene exhibited a most intense IR band at 1160 cm^{-1},

(1) (a) Nakashima, H.; Hashimoto, M.; Sadakane, Y.; Tomohiro, T.; Hatanaka, Y. *J. Am. Chem. Soc.* **2006**, *128*, 15092 and references cited therein. (b) Weber, T.; Brunner, J. *J. Am. Chem. Soc.* **1995**, *117*, 3084. (c) Blencowe, A.; Hayes, W. *Soft Matter* **2005**, *1*, 178.

(2) For general references on photoaffinity labeling, see, for example: (a) Hatanaka, Y.; Sadakane, Y. *Curr. Top. Med. Chem.* **2002**, *2*, 271. (b) Fleming, S. A. *Tetrahedron* **1995**, *51*, 12479. (c) Bayley, H. *Photogenerated Reagents in Biochemistry and Molecular Biology*; Elsevier: Amsterdam, The Netherlands, 1983.

(3) (a) Admasu, A.; Gudmundsdottir, A. D.; Platz, M. S.; Watt, D. S.; Kwiatkowski, S.; Crocker, P. J. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1093. (b) Zuev, P. S.; Sheridan, R. S. *J. Am. Chem. Soc.* **2001**, *123*, 12434. (c) Sander, W. *J. Org. Chem.* **1988**, *53*, 121. (d) Brams, D. L. S.; Dailey, W. P. *Chem. Rev.* **1996**, *96*, 1585. (e) Brunner, J.; Senn, H.; Richards, F. *J. Biol. Chem.* **1980**, *255*, 3313. (f) Turro, N. J.; Butcher, J. A., Jr.; Hefferon, G. J. *Photochem. Photobiol.* **1981**, *34*, 517. (g) Nassal, M. *Liebigs Ann. Chem.* **1983**, 1510. (g) Nassal, M. *J. Am. Chem. Soc.* **1984**, *106*, 7540.

(4) Wasserman, E.; Barash, L.; Yager, W. A. *J. Am. Chem. Soc.* **1965**, *87*, 4974.

(5) (a) Kerdesky, F. A. J.; Basha, A. *Tetrahedron Lett.* **1991**, *32*, 2003. (b) DiMenna, W. S. *Tetrahedron Lett.* **1980**, *21*, 2129.

(6) For a general description of the matrix isolation instrumentation, see: Sheridan, R. S.; Zuev, P. S. *J. Am. Chem. Soc.* **2004**, *126*, 12220 and references cited therein. Irradiation wavelengths were selected by a high-pressure Hg lamp/monochromator assembly, and are ±5 nm. See the Supporting Information for further matrix deposition and irradiation details.

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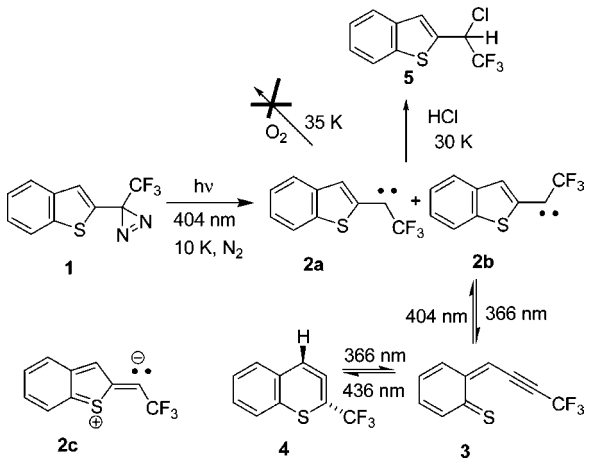
Scheme 1



together with strong absorptions at 490 and 350 nm in the UV/vis spectrum (Figures 1 and 2).

Multiple pieces of evidence indicate that carbene **2**, observed under these conditions, possesses a singlet rather than a triplet ground state. The IR spectrum of **2** (Figure 1) fits best that predicted by B3LYP/6-31+G** calculations for singlet carbene **2a**, with the CF_3 group oriented *syn* to sulfur; IR spectra calculated for triplet **2**, either *syn* or *anti*, as well as those for singlet *anti*-**2b**, were somewhat less satisfactory.[7,8] Similarly, TD B3LYP calculations predict prominent electronic transitions for *syn*-**2a** at 461 ($f = 0.032$) and 321 ($f = 0.37$) nm, which parallel the experimentally observed absorptions (Figure 2). A very weak nπ* transition predicted at 1004 nm ($f = 0.0009$) was not detected. On the other hand, *syn*-triplet **2** is predicted to absorb at 626 ($f = 0.0003$), 530 ($f = 0.013$), 438 ($f = 0.0008$), 401 ($f = 0.018$), and 334 ($f = 0.010$) nm (with very similar transitions for *anti*-triplet).

The reactivity of **2** also is most consistent with singlet rather than triplet multiplicity. Numerous studies have shown that triplet carbenes react readily with O_2 at cryogenic temperatures to give carbonyl oxides.[9] Singlet carbenes are

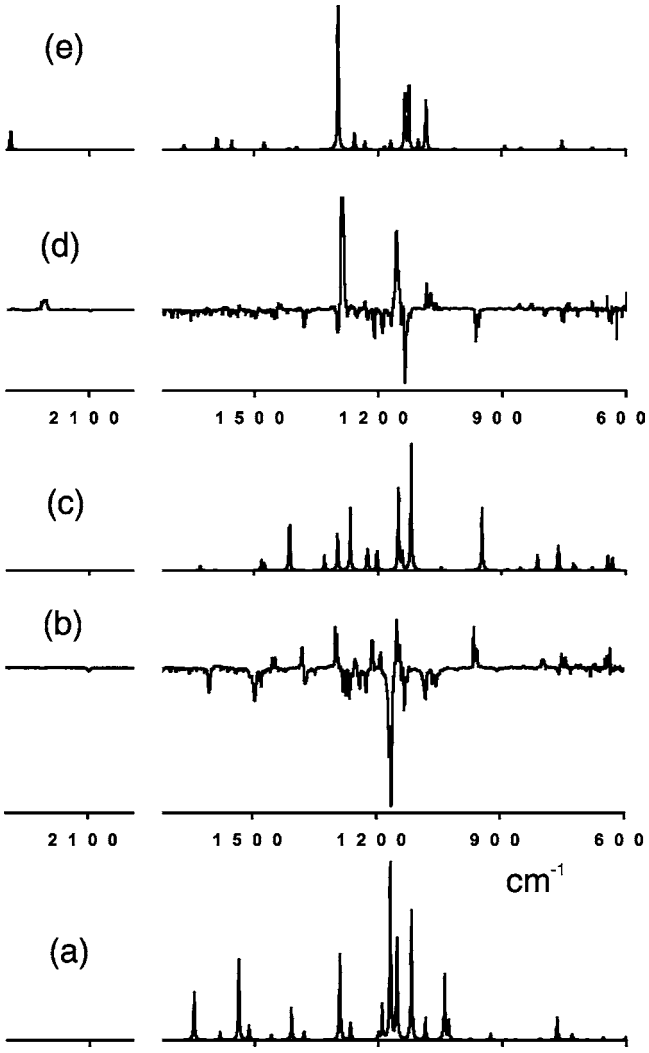


Figure 1. (a) Calculated IR spectrum for singlet *syn*-carbene **2a**. (b) IR difference spectra showing conversion of carbene **2** ("down bands") to allene **4** ("up bands") on 16 h irradiation at 436 nm in N_2 at 10 K. (c) Calculated IR spectrum for allene **4**. (d) IR difference spectra showing conversion of allene **4** ("down bands") to thioquinomethide **3** ("up bands") on 2 h irradiation at 366 nm. (e) Calculated IR spectrum for thioquinomethide **3**. All spectra are displayed with arbitrary absorbance units. Theoretical spectra are from B3LYP/6-31+G** calculations, and frequencies are unscaled.

unreactive under the same conditions. Warming **2** in N_2 matrices doped with relatively high concentrations of O_2 (up to 5%), under conditions where triplet carbenes react rapidly,[9] showed no evidence for reaction.[10] On the other hand, annealing a 2% HCl-doped N_2 matrix containing **2** to 30 K caused disappearance of the carbene IR bands and growth of bands due to the trapped product **5** (by comparison to calculated IR spectra).[8]

(7) All structures were fully optimized by analytical gradient methods using Gaussian 03, Revision C.02: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004. Energies were corrected for zero-point energy differences (ZPVE) (unscaled).

(8) Details of the syntheses, calculations, and several additional theroetical and experimental spectra are given in the Supporting Information.

(9) (a) Sander, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 344. (b) Sander, W.; Bucher, G.; Wierlacher, S. *Chem. Rev.* **1993**, *93*, 1583.

(10) Although matrices are rigid at 10 K, enabling characterization of highly reactive molecules in the presence of small amounts of trapping agents (<5%), warming to approximately 30 K permits diffusion of small dopants. For general details of low-temperature trapping experiments, see, for example: Bally, T. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M. S., Jones, M. J., Jr., Eds.; John Wiley & Sons: Hoboken, NJ, 2004; p 797.

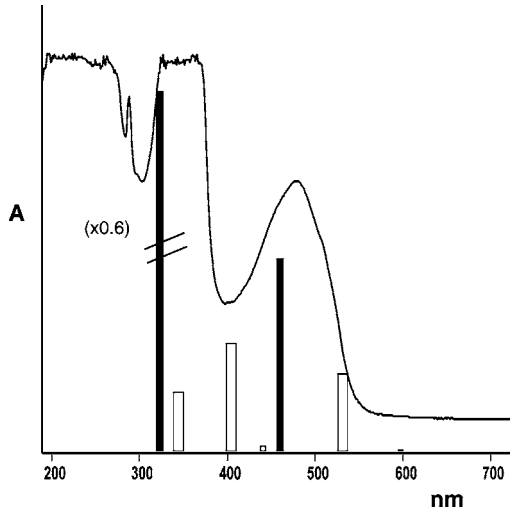


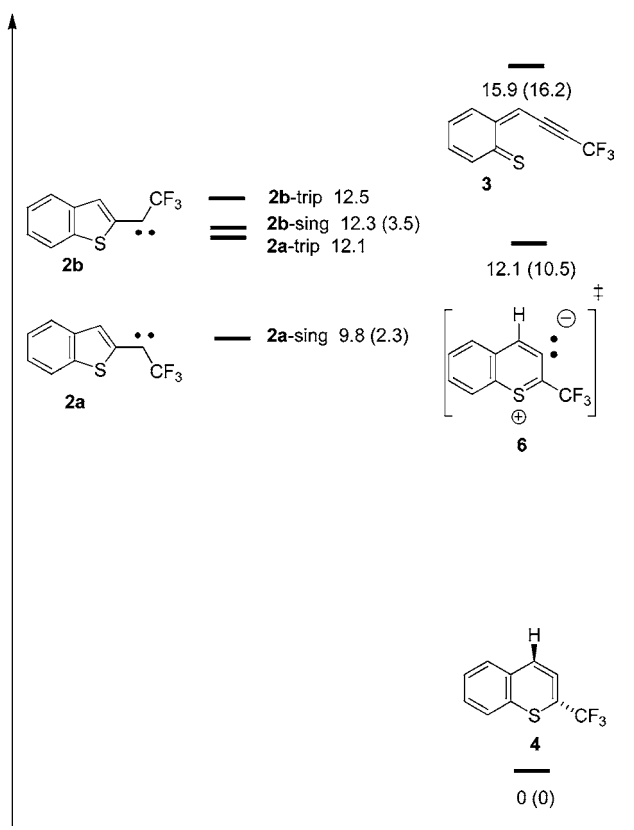
Figure 2. UV/vis spectrum of carbene **2** generated by irradiation of allene **4** matrix isolated in N_2 at 10 K for 2 h at 404 nm. Results of wavelengths and relative intensities predicted by TD B3LYP/6-31+G** calculations are shown for singlet **2a** (filled bars) and triplet **2a** (open bars).[8] The absolute absorbance scale ranges from 0.7 to 3.7 units. See the Supporting Information for the UV/vis spectrum of starting diazirine **1**

As shown in Scheme 2, B3LYP calculations predict that singlet *syn*-**2a** is lower in energy than singlet *anti*-**2b**, and lower than both conformers of the triplet carbene. Since this level of theory has been suggested to overemphasize the stability of triplet carbenes compared to the corresponding singlets by approximately 2 to 3 kcal/mol,[11,12] the singlet−triplet energy gap for *syn*-**2a** is likely greater than the predicted 2.4 kcal/mol. It is tempting to attribute the stabilization of singlet **2** to π-donation from the electron-rich thiophene unit as exemplified by resonance structure **2c**.[13] It should also be noted, however, that calculations indicate that the CF_3 group actually favors singlet carbenes relative to triplets, compared to H.[14]

As we have observed for other five-membered hetereoaryl carbenes,[15] **2** was quite photolabile and readily interconverted with several other intermediates. For example, irradiation of **2** at 436 nm produced a new product, which we attribute to the strained allene **4** by analogy to our previous studies on related systems (Figure 1). The IR spectrum observed for allene **4** fits that predicted by B3LYP calculations. Moreover, matrices containing **4** displayed absorptions at 360 and 410 nm, close to those predicted by TD calculations (353 nm, $f = 0.04$; and 419 nm, $f = 0.03$).[8]

(11) Geise, C. M.; Hadad, C. M. *J. Org. Chem.* **2000**, *65*, 8348.
(12) Woodcock, H. L.; Moran, D.; Brooks, B. R.; Schleyer, P.v.R.; Schaefer, H. F. *J. Am. Chem. Soc.* **2007**, *129*, 3763.
(13) For comparison, preliminary calculations at the same theoretical level predict the *triplet* cyclopentadienyl carbene corresponding to **2a**, where S is replaced by CH_2, to lie 3.8 kcal/mol *below* the singlet. However, the *singlet* benzofuryl carbene (S replaced by O) corresponding to **2a** lies 3.9 kcal/mol below the triplet. Jian Wang, unpublished results.
(14) O'Gara, J. E.; Dailey, W. P. *J. Am. Chem. Soc.* **1994**, *116*, 12016.
(15) (a) Khasanova, T.; Sheridan, R. S. *J. Am. Chem. Soc.* **1998**, *120*, 234. (b) Khasanova, T.; Sheridan, R. S. *J. Am. Chem. Soc.* **2000**, *122*, 8585. (c) Nikitina, A.; Sheridan, R. S. *J. Am. Chem. Soc.* **2002**, *124*, 7670. (d) Nikitina, A.; Sheridan, R. S. *Org. Lett.* **2005**, *7*, 4467.

Scheme 2. Relative B3LYP/6-31+G** Energies (kcal/mol)[a]



[a] Chloro derivatives are given in parentheses.[15d]

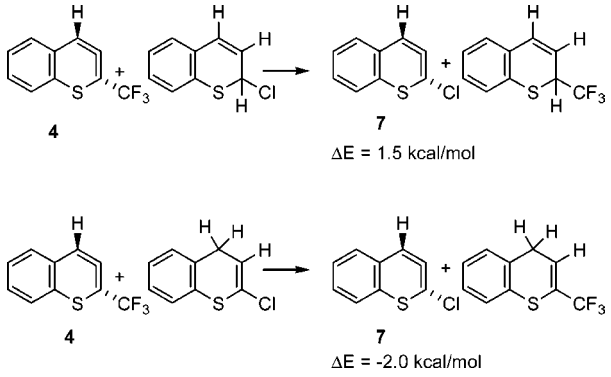
Alternatively, irradiation of a matrix containing **2** (or, likewise, **4**) at 366 nm converted the carbene mainly into the ring-opened thioquinomethide **3**, identified by comparison of the IR spectra to those predicted by B3LYP calculations (Figure 1). At the same time, the UV/vis absorptions attributed to **2** were replaced by strong bands at 510 and 350 nm. TD calculations predict absorptions for **3** at 548 ($f = 0.074$) and 332 ($f = 0.13$) nm, in satisfactory agreement with this assignment.[8]

All three intermediates, **2**, **3**, and **4**, could be interconverted photochemically; any of the isomers could be favored selectively depending on careful control of irradiation wavelength. Thus, irradiation of matrices containing either the thioquinomethide **3** or allene **4** at 404 nm, where carbene **2** absorbs less intensely, cleanly converted them back to carbene. On the other hand, irradiation of the matrices at 366 nm, where **2** and **4** absorb more strongly than thioquinomethide **3**, gave matrices where **3** predominated. Finally, 436 nm pumps the strong absorptions of **2** and **3**, producing mainly allene **4** in the photoequilibria. As we have discussed previously,[15] the ring-opened species **3** offers a logical mechanistic intermediate connecting carbene **2** and allene **4**.

Scheme 2 shows relative energies of the various intermediates in this system resulting from B3LYP calculations.[7,8] It is interesting to compare these results to the chloro-

substituted carbene system that we have reported previously.[15d] As shown, the corresponding singlet chlorocarbenes are considerably lower in energy (in parentheses) relative to the other isomeric intermediates, consistent with the well-recognized stabilizing effect of halogen substitution.[16] On the other hand, the calculations suggest only small differences between the CF_3-allene **4** and the corresponding chloro-compound **7**. Isodesmic calculations shown in Scheme 3 suggest that the inherent instabilities of the strained allenic moieties in **4** and the chloro analogue **7** are comparable.

Scheme 3. Isodesmic Reactions to Compare the B3LYP/6-31+G** Energies of Cl and CF_3 Allenes



Not surprisingly, the theoretically predicted geometries of **4** and the chloroallene[15d] are also quite similar. Hence, H and CF_3 are twisted 145.6° and 150.4°, respectively, out of the plane defined by the three allenic carbons in **4**. Corresponding values for **7** are 156.6° and 146.4° for H and Cl. Similarly, the C=C=C angles for **4** and **7** are 134.9° and 131.8°, respectively. The visible electronic absorbances for **4** and **7**,[15d] due to transition from the HOMO, which has significant lone-pair character on the central allenic carbon, to a π^* LUMO, are very similar at 425 and 410 nm, respectively. Finally, the energy to planarize the trifluoromethyl allene **4**, giving the zwitterionic transition state **6**, is similar to that for the chloroallene **7**.

In conclusion, we have found that **2** is a ground-state singlet, in contrast to previously spectroscopically characterized aryl(trifluoromethyl)carbenes. We tentatively attribute this inversion of favored spin states to π-electron donation of the thiophene moiety in the singlet. Carbene **2**, ring-opened thioquinomethide **3**, and strained cyclic allene **4** have distinct UV/vis absorptions that enable selective generation by careful wavelength control. These results suggest the possibility of new approaches to structural/electronic control of photoaffinity labeling reagents.[1,2]

Acknowledgment. We thank the National Science Foundation (CHE-0456280) for financial support.

Supporting Information Available: Synthetic, spectroscopic, and calculational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Moss, R. A.; Fantina, M. E. *J. Am. Chem. Soc.* **1978**, *100*, 6788.