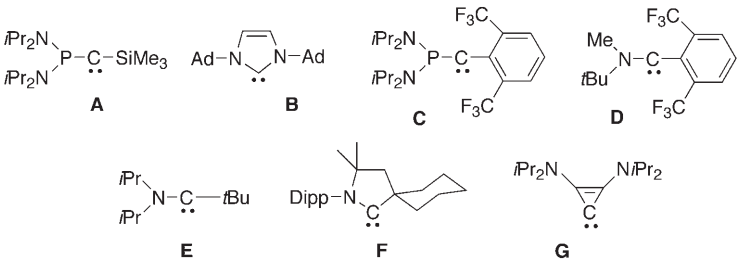
Singlet Carbenes

DOI: 10.1002/anie.200702272

Recently Reported Crystalline Isothiazole Carbenes: Myth or Reality**

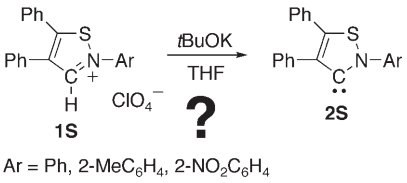
*Alan DeHope, Vincent Lavallo, Bruno Donnadieu, Wolfgang W. Schoeller, and Guy Bertrand**

Following the discovery of the first stable acyclic **A** and cyclic carbenes **B** (Ad = adamantyl) by our group,[1] and Arduengo's group,[2] respectively, several types of singlet[3] carbenes have been isolated.[4] For a long time, it was believed that these electron-deficient species could only be stable when two heteroatoms were directly linked to the carbene center. Even in 2007, it has been written: "To date, all theoretical and experimental evidence indicates that, in order to form a stable carbene, the carbenic carbon needs to be bonded to strong π-donor atoms".[5] Such a statement is misleading since in recent years, our group has reported the synthesis and X-ray crystal structure of carbenes **C**–**F** (Dipp = 2,6-diisopropylphenyl),[6–9]



which feature only one heteroatom substituent. Last year, we even isolated carbene **G**, which has no heteroatom substituent directly linked to the carbene center.[10] Nevertheless, singlet carbenes are not always "bottle-able"![11]

Recently, in a paper entitled "Synthesis of Stable Isothiazole Carbenes",[12] it was claimed that deprotonation of 2-aryl-4,5-diphenylisothiazolium perchlorates **1S** by potassium *tert*-butylate in absolute THF at room temperature (0 °C according to the Supporting Information) provides the stable isothiazol-3-ylidenes **2S**, which can be isolated as yellow crystalline solids (Scheme 1). The authors wrote: "the carbenes are stable in solution and in the crystal". The stability of derivatives **2S** allowed their characterization by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and even melting points were reported. However, despite their crystalline nature, single crystal diffraction studies were not performed. It was mentioned that the observed ^{13}C NMR signal for the carbene carbon atom of **2S** (δ = 194.3–195.7 ppm) corresponds to the shifts observed for imidazol-2-ylidenes. This statement is correct; however, since the ^{13}C NMR signal for carbenes featuring a nitrogen and a carbon substituent (such as **D**–**F**) appears usually at much lower field,[7–9] these values were somewhat surprising.



Ar = Ph, 2-MeC$_6$H$_4$, 2-NO$_2$C$_6$H$_4$

Scheme 1. Synthesis of isothiazole carbenes as reported in reference [12].

The reported stability of carbenes **2S** was even more unexpected since, four decades ago, Woodward[13a] and Woodman[13b] reported the formation of ketoketenimines **4O** in the deprotonation of 3-unsubstituted isoxazolium salts **1O**, the oxygen analogues of heterocycles **1S**. Indeed, considering the ylidic structure of the putative carbene **2O** (and of course **2S**), one can readily imagine a very simple ring-opening process (Scheme 2).

Scheme 2. Deprotonation of isoxazolium salts **1O** leads to ketoketenimines **4O** by ring opening of transient carbenes **2O** (reference [13]).

We performed calculations at B3LYP/6-311 g** level plus zero-point vibrational-energy correction within the harmonic approximation[14] for the reported carbene **2S** (Ar = Ph) and its possible thioketoketenimine isomer **4S(s-*cis*)** (Figure 1). The latter did not appear to be an energy minimum; it undergoes a ring closure into its 2-imino-2*H*-thiete isomer **3S**, which is 21.7 kcal mol^{-1} more stable than carbene **2S**. Interestingly, although carbene **2S** is an energy minimum, a transition state **TS** for the rearrangement **2S**→**3S** was located only 1.0 kcal mol^{-1} higher in energy than carbene **2S**, obviously precluding the isolation of the latter. To be complete, we also investigated the *trans* thioketoketenimine **4S(s-*trans*)**,

[*] A. DeHope, V. Lavallo, B. Donnadieu, Prof. W. W. Schoeller, Prof. G. Bertrand
UCR-CNRS Joint Research Chemistry Laboratory (UMI 2957)
Department of Chemistry
University of California
Riverside, CA 92521-0403 (USA)
Fax: (+1) 951-827-2725
E-mail: gbertran@mail.ucr.edu

[**] We are grateful to the NSF (CHE 0518675) for financial support of this work.

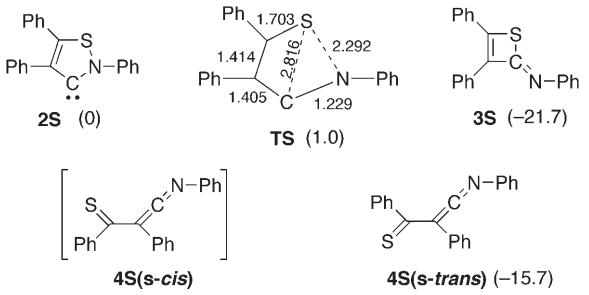
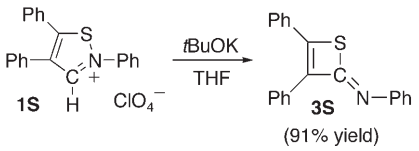


Figure 1. Different isomers of isothiazole carbene **2S** with their relative energies (kcal mol^{-1}) in parentheses, and geometry (interatomic distances in Å) of the transition state (**TS**) for the rearrangement **2S**→**3S**.

which appeared to be 6.0 kcal mol^{-1} higher in energy than the four-membered heterocycle **3S**.

We prepared the 2,4,5-triphenylisothiazolium perchlorate **1S** (Ar = Ph)[15] and carried out the deprotonation reaction under the experimental conditions described in the original paper.[12] After filtration of the reaction mixture and evaporation of the solvent and *tert*-butyl alcohol, 2-imino-2*H*-thiete **3S** was the only observable species (Scheme 3). This heterocycle[16] was isolated in 91% yield and fully characterized including by a single-crystal X-ray diffraction study (Figure 2).[17] As predicted by calculations, monitoring the reaction by ^{13}C NMR spectroscopy did not allow the observation of any intermediates; moreover no signal in the range reported for the carbene carbon of **2S** was observed.



Scheme 3. Deprotonation of triphenylisothiazolium perchlorate **1S** leads to the corresponding 2-imino-2*H*-thiete **3S**.

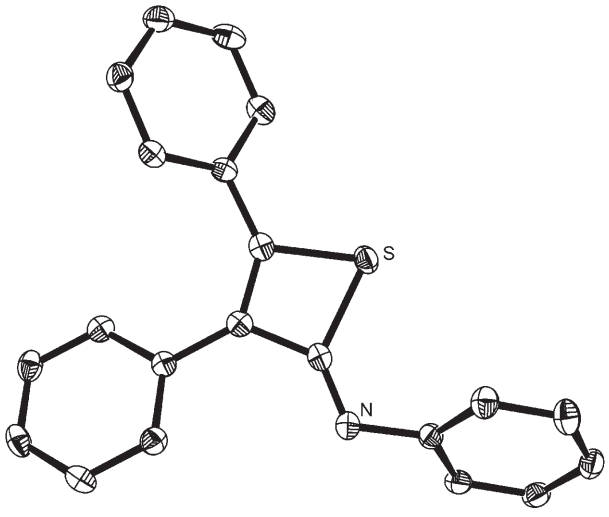
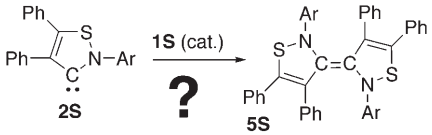


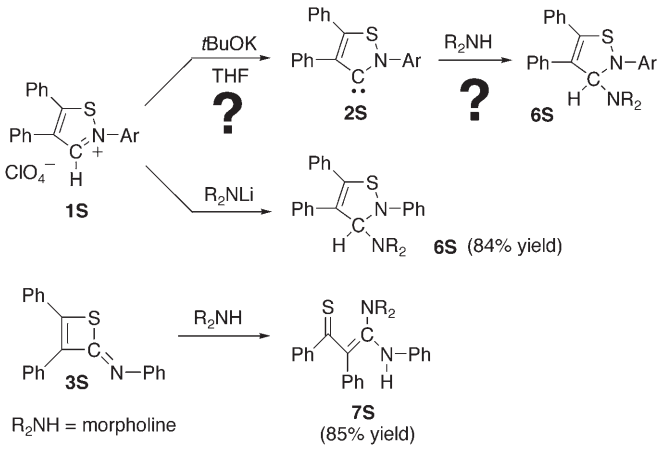
Figure 2. Molecular structure of 2-imino-2*H*-thiete **3S** in the solid state. Thermal ellipsoids represent 50% probability.

To bring evidence for the carbene nature of their products, the authors first claimed that addition of some crystals of isothiazolium perchlorate **1S** to the "carbenes" **2S** in THF afforded the carbene dimers **5S** with an *E* configuration (Scheme 4).[12] Since the two substituents of the carbene have similar steric bulk, the formation of only one stereoisomer is very unlikely.[18] Despite their crystalline nature, the "dimers" have only been characterized by ^{1}H and ^{13}C NMR spectroscopy, as well as mass spectrometry. Assuming the presence of only one isomer, at least 15 ^{13}C NMR signals are expected, all of them in the same range, which makes any attributions highly debatable. Since the "carbenes" **2S** do not exist, we have of course not been able to reproduce the reported results.



Scheme 4. Formation of carbene dimer **5S** as reported in reference [12].

The authors reported that morpholine and piperidine react with isothiazolium salts **1S**, in the presence of potassium *tert*-butylate to give adducts **6S**, which have been fully characterized (including by a single-crystal X-ray diffraction study in the case of piperidine).[12] They explained these results as follows: "Evidently, the transient isothiazol-3-ylidenes react in situ with morpholine in a typical insertion reaction into the polarized NH bond". However, an alternative rationalization for the formation of adducts **6S** is that in the presence of potassium *tert*-butylate, the amines undergo a base-assisted addition to the isothiazolium perchlorate **1S**. We carried out the reaction of **1S** (Ar = Ph) with the lithium salt of morpholine and cleanly obtained adduct **6S** (84% yield) (Scheme 5). Since the authors stated that the amine adducts "can also be obtained directly from the correspond-



Scheme 5. Addition of morpholine to carbene **2S** as reported in reference [12] (top); nucleophilic addition of morpholine lithium salt to **1S** leads to adduct **6S** (middle); addition of morpholine to 2-imino-2*H*-thiete **3S** affords **7S** (bottom).

ing stable carbenes", we added morpholine at room temperature to the heterocycle **3S**. A clean reaction occurred, but instead of derivative **6S**, we isolated compound **7S** (85% yield) resulting from the aminolysis of the C–S bond of **3S** (Scheme 5). Single crystals of zwitterion **7S** were subjected to an X-ray diffraction study (Figure 3).

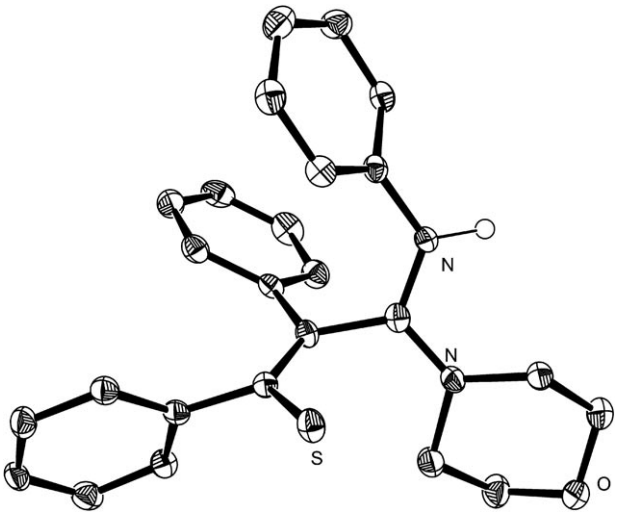


Figure 3. Molecular structure of **7S** in the solid state. Thermal ellipsoids represent 50% probability.

In contrast to recent claims,[12] our calculations and experiments show that 1) isothiazole carbenes **2S** cannot be isolated or even observed at room temperature; 2) they isomerize into their 2-imino-2*H*-thiete isomers **3S** via a transition state **TS** located only about 1 kcal mol^{-1} higher in energy than carbenes **2S**; 3) in contrast to the original findings, no signals about 190 ppm were observed when monitoring by ^{13}C NMR spectroscopy the deprotonation of 2,4,5-triphenylisothiazolium perchlorate **1S**; 4) the formation of carbene dimers **5S** is doubtful, and in any case impossible starting from the free carbene **2S**, since the latter cannot be isolated; 5) for the same reasons, the "carbene–amine adducts" **6S** cannot be prepared from carbenes **2S**, but can be formed by nucleophilic addition to the cationic precursors **1**.

Experimental Section

All manipulations were performed under argon by using standard Schlenk techniques and oven-dried glassware. Dry, oxygen-free solvents were employed. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 spectrometers.

Deprotonation of 2,4,5-triphenylisothiazolium perchlorate (**1S**): A solution of potassium *tert*-butylate (264 mg, 2.36 mmol) in THF was added at 0 °C to a suspension of isothiazolium perchlorate **1S** (835 mg, 2.02 mmol) in THF. The reaction mixture was stirred at 0 °C for 30 minutes. The solvent and *tert*-butyl alcohol was removed, and the residue was extracted with hexanes. After evaporation of hexanes, 2-imino-2*H*-thiete **3S** was obtained as an orange crystalline solid. Yield: 91%; m.p.: 123 °C (reported[16] 124 °C). The spectroscopic data are similar to those already reported.[16]

Addition of morpholine lithium salt to triphenylisothiazolium perchlorate **1S**: A solution of morpholine lithium salt (prepared by reaction of *n*BuLi with morpholine) (129 mg, 1.39 mmol) in THF was added at −78 °C to a stirred suspension of isothiazolium perchlorate **1S** (487 mg, 1.39 mmol) in THF. The reaction mixture was warmed to room temperature and stirred for 30 minutes. After the solvent was removed and the residue was extracted with hexanes, **6S** was obtained as a crystalline solid. Yield: 84%; m.p.: 117 °C (reported[12] 117 °C). The spectroscopic data are similar to those already reported.[12]

Addition of morpholine to 2-imino-2*H*-thiete **3S**: Morpholine (0.2 mL, 2.23 mmol) was added at 0 °C by syringe to a stirred solution of **3S** (140 mg, 0.45 mmol) in THF. The reaction mixture was stirred at room temperature for 1 h, and then the solvent was removed to yield a yellow solid. Recrystallization from 5:1 hexanes/THF at room temperature afforded **7S** as yellow crystals. Yield: 85%; m.p.: 186 °C.

Received: May 23, 2007
Published online: July 27, 2007

Keywords: carbenes · heterocycles · ring-opening reactions

[1] a) A. Igau, H. Grützmacher, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* **1988**, *110*, 6463–6466; b) A. Igau, A. Baceiredo, G. Trinquier, G. Bertrand, *Angew. Chem.* **1989**, *101*, 617–618; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 621–622.

[2] a) A. J. Arduengo III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361–363; b) A. J. Arduengo III, *Acc. Chem. Res.* **1999**, *32*, 913–921.

[3] Persistent triplet carbenes have also been prepared: a) M. Kawano, K. Hirai, H. Tomioka, Y. Ohashi, *J. Am. Chem. Soc.* **2007**, *129*, 2383–2391; b) T. Itoh, Y. Nakata, K. Hirai, H. Tomioka, *J. Am. Chem. Soc.* **2006**, *128*, 957–967; c) E. Iwamoto, K. Hirai, H. Tomioka, *J. Am. Chem. Soc.* **2003**, *125*, 14664–14665; H. Tomioka, E. Iwamoto, H. Itakura, K. Hirai, *Nature* **2001**, *412*, 626–628.

[4] Reviews on stable singlet carbenes: a) S. P. Nolan, *N-Heterocyclic Carbenes in Synthesis*, Wiley-VCH, **2006**; b) "N-Heterocyclic Carbenes in Transition Metal Catalysis": F. Glorius, *Top. Organomet. Chem.* **2006**, *21*; c) F. E. Hahn, *Angew. Chem.* **2006**, *118*, 1374–1378; *Angew. Chem. Int. Ed.* **2006**, *45*, 1348–1352; d) N. Kuhn, A. Al-Sheikh, *Coord. Chem. Rev.* **2005**, *249*, 829–857; e) E. Peris, R. H. Crabtree, *Coord. Chem. Rev.* **2004**, *248*, 2239–2246; f) C. M. Crudden, D. P. Allen, *Coord. Chem. Rev.* **2004**, *248*, 2247–2273; g) W. Kirmse, *Angew. Chem.* **2004**, *116*, 1799–1801; *Angew. Chem. Int. Ed.* **2004**, *43*, 1767–1769; h) R. W. Alder, M. E. Blake, M. E Chaker, J. N. Harvey, F. Paolini, J. Schütz, *Angew. Chem.* **2004**, *116*, 6020–6036; *Angew. Chem. Int. Ed.* **2004**, *43*, 5896–5911; i) Y. Canac, M. Soleilhavoup, S. Conejero, G. Bertrand, *J. Organomet. Chem.* **2004**, *689*, 3857–3865; j) D. Bourissou, O. Guerret, F. P. Gabbaï, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39–92.

[5] S. Diez-Gonzalez, S. P. Nolan, *Coord. Chem. Rev.* **2007**, *251*, 874–883.

[6] a) C. Buron, H. Gornitzka, V. Romanenko, G. Bertrand, *Science* **2000**, *288*, 834–836; b) E. Despagnet, K. Miqueu, H. Gornitzka, P. W. Dyer, D. Bourissou, G. Bertrand, *J. Am. Chem. Soc.* **2002**, *124*, 11834–11835.

[7] a) S. Sole, H. Gornitzka, W. W. Schoeller, D. Bourissou, G. Bertrand, *Science* **2001**, *292*, 1901–1903; b) X. Cattoen, H. Gornitzka, D. Bourissou, G. Bertrand, *J. Am. Chem. Soc.* **2004**, *126*, 1342–1343.

[8] V. Lavallo, J. Mafhouz, Y. Canac, B. Donnadieu, W. W. Schoeller, G. Bertrand, *J. Am. Chem. Soc.* **2004**, *126*, 8670–8671.

[9] a) V. Lavallo, Y. Canac, C. Präsang, B. Donnadieu, G. Bertrand, *Angew. Chem.* **2005**, *117*, 5851–5855; *Angew. Chem. Int. Ed.* **2005**, *44*, 5705–5709; b) V. Lavallo, Y. Canac, A. Dehope, B.

Donnadieu, G. Bertrand, *Angew. Chem.* **2005**, *117*, 7402 – 7405; *Angew. Chem. Int. Ed.* **2005**, *44*, 7236 – 7239; c) R. Jazzar, R. D. Dewhurst, J. B. Bourg, B. Donnadieu, Y. Canac, G. Bertrand, *Angew. Chem.* **2007**, *119*, 2957 – 2960; *Angew. Chem. Int. Ed.* **2007**, *46*, 2899 – 2902; d) G. D. Frey, V. Lavallo, B. Donnadieu, W. W. Schoeller, G. Bertrand, *Science* **2007**, *316*, 439 – 441.

[10] a) V. Lavallo, Y. Canac, B. Donnadieu, W. W. Schoeller, G. Bertrand, *Science* **2006**, *312*, 722 – 724; b) V. Lavallo, Y. Ishida, B. Donnadieu, G. Bertrand, *Angew. Chem.* **2006**, *118*, 6804 – 6807; *Angew. Chem. Int. Ed.* **2006**, *45*, 6652 – 6655.

[11] *Reactive Intermediate Chemistry* (Eds.: M. Jones, R. A. Moss), Wiley-Interscience, New York, **2004**.

[12] J. Wolf, W. Böhlmann, M. Findeisen, T. Gelbrich, H. J. Fofmann, B. Schulze, *Angew. Chem.* **2007**, *119*, 3179 – 3182; *Angew. Chem. Int. Ed.* **2007**, *46*, 3118 – 3121.

[13] a) R. B. Woodward, D. J. Woodman, *J. Am. Chem. Soc.* **1966**, *88*, 3169 – 3170; b) D. J. Woodman, A. I. Davidson, *J. Org. Chem.* **1973**, *38*, 4288 – 4295.

[14] M. J. Frisch et al., Gaussian 03 (Revision C.02), Gaussian, Wallingford CT, **2004**.

[15] a) B. Schulze, K. Rosenbaum, J. Hilbig, L. Weber, *J. Prakt. Chem./Chem.-Ztg.* **1992**, *334*, 25 – 33; b) B. Schulze, U. Obst, G. Zahn, B. Friederich, R. Cimiraglia, H. J. Hofmann, *J. Prakt. Chem./Chem.-Ztg.* **1995**, *337*, 175 – 183; c) J. Fahrig, T. H. E. Freysoldt, C. Hartung, J. Sieler, B. Schulze, *J. Sulfur Chem.* **2005**, *26*, 211 – 224.

[16] Compound **3S** has already been prepared by another route, and the reported spectroscopic data are similar to those observed in this work: J. Goerdeler, M. Yunis, H. Puff, A. Roloff, *Chem. Ber.* **1986**, *119*, 162 – 168.

[17] CCDC 648163 (**3S**), and CCDC 648164 (**7S**) 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.

[18] a) F. E. Hahn, M. Paas, D. Le Van, T. Lugger, *Angew. Chem.* **2003**, *115*, 5402 – 5406; *Angew. Chem. Int. Ed.* **2003**, *42*, 5243 – 5246; b) F. E. Hahn, M. Paas, D. Le Van, R. Frohlich, *Chem. Eur. J.* **2005**, *11*, 5080 – 5085; c) S. Conejero, Y. Canac, F. S. Tham, G. Bertrand, *Angew. Chem.* **2004**, *116*, 4181 – 4185; *Angew. Chem. Int. Ed.* **2004**, *43*, 4089 – 4093.

