Stable Carbenes

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Synthesis of Stable Isothiazole Carbenes

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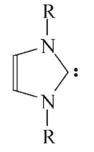
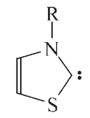
Dedicated to Professor Peter Welzel on the occasion of his 70th birthday

An important step in our understanding of the structure and reactivity of carbenes was the isolation of heteroatom-substituted singlet carbenes.[1] On the basis of an idea of Wanzlick and co-workers[2a,b] to stabilize carbenes through the presence of amino substituents, Arduengo et al. prepared the first crystalline carbene, 1,3-di(1-adamantyl)imidazol-2-ylidene (**1**), in 1991.[3a] Carbenes of the type **1** experience some aromatic stabilization.[4] In the past 15 years, the number of such carbenes has continuously increased.[1–3,5] Besides imidazol-2-ylidenes of the type **1**, 1,3-thiazol-2-ylidenes **2**[6] and 1,2,4-triazol-3-ylidenes **3**[1a,6e,7] have also been obtained.


R = adamantyl

1


R = alkyl, aryl

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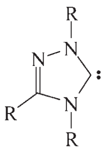
R = alkyl, aryl

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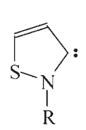
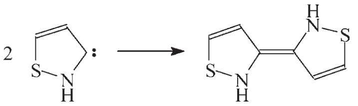

R = aryl

4

In comparison with the relatively great number of stable carbenes of the types **1**–**3**, there are only a few stable acyclic and nonconjugated cyclic carbenes.[2c–f] Whereas stable imidazolyl-2- and 1,3-thiazol-2-ylidenes are accessible, isothiazol-3-ylidenes **4** could not be isolated until now. This is not surprising when one compares some thermodynamic and kinetic characteristics for typical carbene reactions of **1**, **2**, and **4** (R = H) estimated by means of ab initio calculations (for the details of the quantum chemical calculations, see the Supporting Information). The reaction enthalpies and free reaction enthalpies for the carbene dimerization (Table 1) indicate that the tendency to form dimers is much higher for the singlet isothiazol-3-ylidenes than for the other types of heterocyclic carbenes. Hints of the lower stability of the isothiazol-3-ylidenes can also be obtained from the calculated free reaction enthalpies and free activation enthalpies (Table 2) for the interconversion between carbenes and the

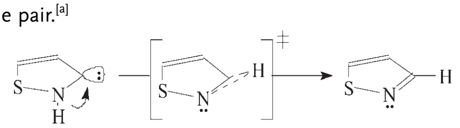
Table 1: Reaction and free reaction enthalpies [kcal mol^{-1}] for the dimerization of the isothiazole singlet carbene and its 2-aryl-4,5-diphenyl derivative.[a]



Ylidene	Δ*H*	Δ*G*
imidazol-2-	−15.2	−3.2
thiazol-2-	−38.2	−27.0
isothiazol-3-	−50.2	−37.3
2-aryl-4,5-diphenyl-isothiazol-3-	−34.1	−20.1

[a] In comparison with the corresponding data for the singlet carbenes of imidazole and thiazole estimated at the B3LYP/6-31G* level of ab initio MO theory. See also references [1c] and [8].

Table 2: Free reaction enthalpies and free activation enthalpies [kcal mol^{-1}] for the 2,3-hydrogen migration in the isothiazol-3-ylidene/isothiazole pair.[a]



Ylidene	Δ*G*	Δ*G*$^{\neq}$
imidazol-2-	−30.1	40.9
thiazol-2-	−32.7	42.2
isothiazol-3-	−41.0	33.5

[a] In comparison with the 1,2-hydrogen migration in the imidazol-2-ylidene/imidazole and thiazol-2-ylidene/thiazole pairs, estimated at the B3LYP/6-31G* level of ab initio MO theory.

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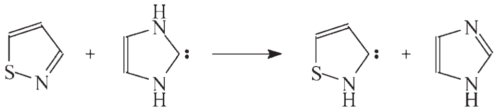
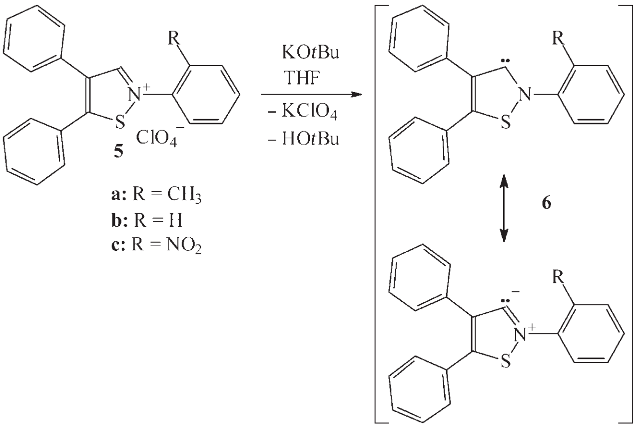
basic heterocycles by 1,2- and 2,3-migration of a hydrogen atom via a nonplanar transition state. The data demonstrate that the formation of isothiazole carbenes is disfavored on both thermodynamic and kinetic grounds.

The data on mutual isodesmic reactions between the various heterocycles and their singlet carbenes confirm these tendencies. Thus, the free reaction enthalpy for the reaction of isothiazole with imidazol-2-ylidene to give isothiazol-3-ylidene and imidazole according to Scheme 1 is 10.9 kcal mol^{-1} and that for the analogous reaction of isothiazole and thiazol-2-ylidene to give isothiazol-3-ylidene and thiazole is 8.3 kcal mol^{-1}. The stability of isothiazol-3-ylidenes can be increased by ring substitution. For example, the calculated dimerization energies of 2-aryl-4,5-diphenyl-substituted isothiazoles are comparable to those of imidazol- and thiazolylidenes (Table 1).



Scheme 1. Isodesmic reaction between the isothiazole/imidazole heterocycles and their singlet carbenes.

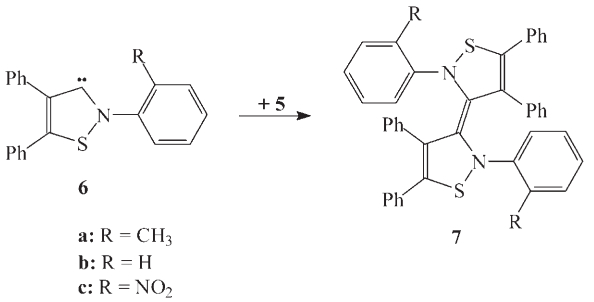
Herein, we report the synthesis of the first stable singlet isothiazol-3-ylidenes **6** obtained by deprotonation of isothiazolium perchlorates **5** (for the details of the synthesis, see the Supporting Information). The isothiazolium salts **5** are available by intramolecular cyclocondensation of 2,3-diphenyl-3-thiocyanatoprop-2-enal and anilines in the presence of perchloric acid.[9,10] It has long been known that isothiazolium salts bearing 5-methyl or 5-methylene groups at the isothiazole ring react with amines to give thiadiazapentalenes,[9,11] spirocyclic isothiazolium salts,[12] and thianthrenes.[12a] The deprotonation of the 2-aryl-4,5-diphenylisothiazolium perchlorates **5a–c** by potassium *tert*-butylate in absolute tetrahydrofuran (THF) at room temperature provides the stable 2-aryl-4,5-diphenylisothiazol-3-ylidenes **6a–c** (R = CH_3, H, and NO_2) upon elimination of potassium perchlorate and *tert*-butyl alcohol (Scheme 2). The pure ylidenes **6** are yellow crystalline solids (see the Supporting Information).



Scheme 2. Synthesis of **6a–c** from **5a–c** by deprotonation.

The carbene structure of **6a–c** was confirmed by solid-state and solution NMR studies. The ^{13}C NMR chemical shifts for the carbene carbon atoms in solution lie in the range between $\delta = 194.3$ and 195.7 ppm. The solid-state ^{13}C NMR chemical shifts are between $\delta = 191.7$ and 201.4 ppm. These values correspond to the shifts observed for imidazol-2-ylidenes, whereas a signal at $\delta = 254.3$ ppm was observed for 1,3-thiazol-2-ylidenes.[6a] The fact that the ^{13}C CP-MAS NMR measurements (CP = cross polarization; MAS = magic angle spinning) could be performed is proof that the carbenes are stable in solution and in the crystal. The generation of carbene can be monitored in situ by the ^{13}C NMR signals emerging at $\delta = 194.0$–194.8 ppm for the C-3 atom. The signals for the parent ion in the mass spectra correspond to the expected carbene masses.

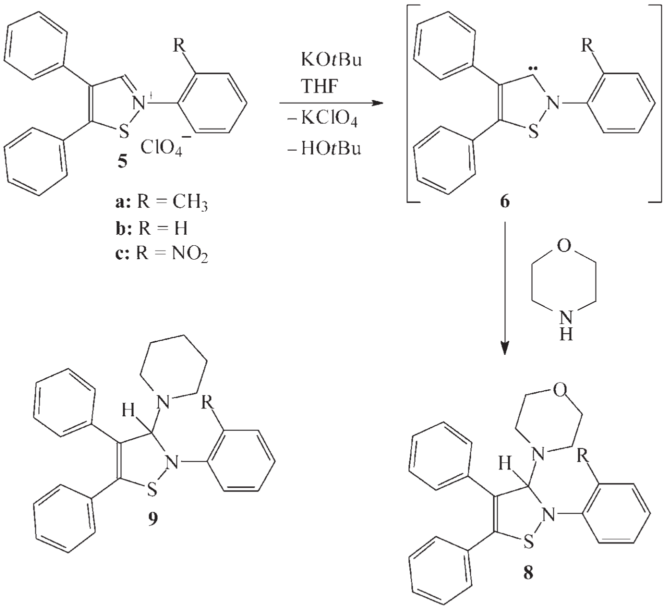
All isolated isothiazol-3-ylidenes **6** undergo typical carbene reactions. They dimerize to give the derivatives **7a-c** (R = CH_3, H, and NO_2) according to Scheme 3 (see also the Experimental Section). The free dimerization enthalpies for **7a**, **b**, and **c** calculated at the B3LYP/6-31G* level are −15.8 kcal mol^{-1}, −20.1 kcal mol^{-1}, and −25.7 kcal mol^{-1}, respectively, thus indicating that the 2-(*o*-tolyl)-substituted carbene **6a** is more stable than the unsubstituted and *o*-nitro derivatives (see also Table 1).



Scheme 3. Synthesis of the isothiazol-3-ylidene dimers **7a–c**.

The isothiazolium perchlorates **5** provide isothiazol-3-ylmorpholines **8** in the presence of potassium *tert*-butylate in absolute THF. Evidently, the transient isothiazol-3-ylidenes react in situ with morpholine in a typical insertion reaction into the polarized NH bond (Scheme 4) leading to the morpholino derivatives **8a–c** (R = CH_3, H, and NO_2; see the Experimental Section and the Supporting Information). Such reactions occur also as side reactions in the carbene synthesis itself, as can be shown by NMR measurements. Thus, the carbenes attack in situ the *tert*-butyl alcohol that results from the *tert*-butylate employed for the deprotonation. In the case of carbene **6c**, ^{13}C NMR signals emerge at $\delta = 102.2$ (C-3), 76.2 ($OC(CH_3)_3$), and 31.6 ppm (CH_3), which correspond to the 3-*tert*-butoxyisothiazole derivative.

Analogous to the reaction with morpholine, the salts **5** react also with piperidine in the presence of potassium *tert*-butylate via the in situ formed isothiazole carbenes **6** to give isothiazol-3-yl-piperidines **9** in very good yields. Both **8** and **9** can also be obtained directly from the corresponding stable carbenes **6**.



Scheme 4. Synthesis of isothiazol-3-ylmorpholines **8** and -piperidines **9** from isothiazolium perchlorates **5** via transient isothiazol-3-carbenes **6**.

The X-ray crystal structure[13] of the piperidine derivative **9c** (R = NO$_2$), shown in Figure 1, is representative of the structure of all morpholino and piperidino derivatives and supports the carbene character of the intermediates **6a–c** involved in the synthesis of **8** and **9**.

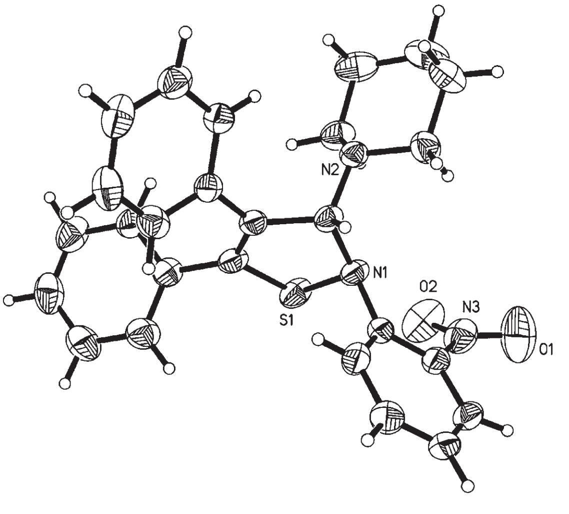


Figure 1. X-ray crystal structure of **9c** (50% probability for thermal ellipsoids).[13]

In conclusion, stable singlet isothiazole carbenes **6** have been obtained for the first time by deprotonation of isothiazolium salts **5**. The wide variety of carbene reactions offers numerous possibilities for further syntheses, which are currently being investigated.

Experimental Section

Melting points (corrected) were determined on a Boetius micromelting-point apparatus. The ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini-200, and -300, as well as Bruker Avance DRX-400, -600, and -700 spectrometers with tetramethylsilane as an internal standard. Solid-state ^{13}C CP-MAS NMR experiments were performed on a Bruker MSL 500 spectrometer at a resonance frequency of 125.75 MHz with a pulse length of 5.9 µs, a mixing time of 3 ms, and a recycle delay of 5 s; 6000 scans were measured for each spectrum. The samples were spun in a 4-mm Zirconia rotor at a frequency of 12 kHz. All spectra were referenced against adamantane as external standard. The mass spectra were determined on a Quadrupole mass spectrometer VG 12-250 at 70 eV. The elemental analyses were performed on a Heraeus CHNO Rapid Analyzer, and the obtained data agree well with the calculated values. The details of the syntheses and the quantum chemical calculations, as well as the characteristics of the compounds are given in the Supporting Information.

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Keywords: ab initio calculations · carbene reactions · carbenes · heterocycles

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[13] Crystal data for **9c** ($C_{26}H_{25}N_3O_2S$): $M_r = 443.55$, $T = 213(2)$ K, crystal size $0.10 \times 0.10 \times 0.10$ mm^3, monoclinic, space group $C2/c$, $a = 19.4634(12)$, $b = 14.3484(9)$, $c = 18.7290(13)$ Å, $\beta = 115.920(7)°$, $V = 4704.3(5)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.253$ Mg m^{-3}, $\mu = 0.165$ mm^{-1}, range for data collection 2.33–28.03 mm^3, index ranges $-25 \leq h \leq 25$, $-18 \leq k \leq 18$, $-24 \leq l \leq 24$, reflections collected 22 404, independent reflections 5646 [$R_{int} = 0.0631$], max./min. transmission 0.9837/0.9837, final R indices [$I > 2\sigma(I)$] $R^1 = 0.0352$, $wR^2 = 0.0646$, R indices (all data) $R^1 = 0.0944$, $wR^2 = 0.0719$, min./max. residual electron density 0.171/−0.168 e Å^{-3}. Data were collected on an IPDS1 diffractometer (Fa. STDE) with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) at 293 K with the ϕ scan technique. Empirical absorption corrections were applied. The structure was solved by direct methods and refined by the full-matrix least-squares method on F^2 with SHELXTL-97 software. Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre, CCDC 629611 (**9c**) contains 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.