DOI: 10.1002/ejoc.200900069

Lessons of 3-Alkoxy-4-(*p*-chlorophenyl)-1,3-thiazole-2(3*H*)-thione Chemistry Learned from Structural Investigations

Jens Hartung,*[a] Kristina Daniel,[a] Uwe Bergsträßer,[a] Irina Kempter,[a] Nina Schneiders,[a] Steffen Danner,[a] Philipp Schmidt,[b] Ingrid Svoboda,[c] and Hartmut Fuess[c]

Keywords: Radicals / Heterocycles / Isomerization / Molecular modeling / Rearrangement / Sulfur

Synthetic, spectroscopic, and structural investigations provided evidence that distinguished neat 3-alkoxy-4-(*p*-chlorophenyl)-1,3-thiazole-2(3*H*)-thiones (CPTTORs), once developed to serve as alkoxyl radical precursors for storage and use on demand, showed background reactivity. Selectivity in these transformations was guided by the nature of the *O*-alkyl substituent. Two pathways reflected the inherent weakness of the N,O bond, leading to products of isomerization and rearrangement. In a third instance, methyl translocation from oxygen to sulfur occurred to furnish a heteroaromatic *N*-oxide at the expense of a cross conjugated π-system. Consistent X-ray crystallographic data sets served as a basis for electronic structure method assessment in order to model aspects relevant to structure and decomposition chemistry that were not available from diffraction data.

Introduction

3-Alkoxy-4-(*p*-chlorophenyl)-1,3-thiazole-2(3*H*)-thiones (CPTTORs; e.g., **1a**–**d**; Figure 1) were introduced in 1997 as reagents for alkoxyl radical generation in the absence of strong oxidants and metal ions at neutral pH.[1–3] The compounds are available in a straightforward manner through *O*-alkylation of the acid CPTTOH,[4,5] which in turn can be prepared in ca. 75 g batches according to a well-elaborated protocol.[6] CPTTORs very effectively liberate oxygen-centered radicals through N,O bond homolysis upon photochemical excitation ($\lambda \geq 350$ nm), microwave irradiation (2.45 GHz), or heating (≈80–120 °C) in the presence of an initiator.[7] Their application contributed to progress in various fields of mechanistic,[8–10] photobiological,[11] and synthetic alkoxyl radical chemistry.[5,12,13]

CPTTORs form colorless solids that can be stored and applied on demand.[14–16] In samples of heterocycles **1a**–**d**, which had been kept for extended periods of time, new products unexpectedly appeared. As no comprehensive systematic study on *O*-alkyl thiohydroxamate reactivity existed for classifying observed transformations, the new products were separated and characterized in a combined spectroscopic, synthetic, and X-ray crystallographic study. Energetic aspects of CPTTOR reactivity that were not available from structural and spectroscopic investigations were deduced from model density functional theory calculations. The lessons learned thereby showed that distinguished neat CPTTORs selectively decomposed by (i) isomerization, (ii) rearrangement, or (iii) fragmentation. None of the compounds formed in the course of these reactions, however, had the potential to serve as potent inhibitor for radical chain reactions.

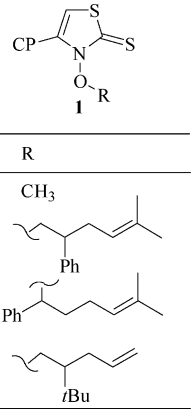


Figure 1. Structure formulae and indexing of 3-alkoxy-4-(*p*-chlorophenyl)-1,3-thiazole-2(3*H*)-thiones (CPTTOR) relevant for the present study (CP = *p*-ClC_6H_4).

[a] Fachbereich Chemie, Organische Chemie, Technische Universität Kaiserslautern,
Erwin-Schrödinger-Straße, 67663 Kaiserslautern, Germany
Fax: +49-631-205-3921
E-mail: hartung@chemie.uni-kl.de
[b] Institut für Organische Chemie, Universität Würzburg,
Am Hubland, 97074 Würzburg, Germany
[c] Technische Universität Darmstadt, Strukturforschung, FB11 Material- und Geowissenschaften,
Petersenstr. 23, 64287 Darmstadt, Germany

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900069.

Results and Interpretation

Lesson 1: X-ray Crystallography, Electronic Structure Methods, and Conformational Analysis

The propensity of CPTTORs to crystallize in combination with a noteworthy stability toward X-rays allowed the fundamentals of *O*-alkyl thiohydroxamate solid state chemistry to be systematically explored as a basis for subsequent computational studies on structure and reactivity. Attempts to crystallize CPTTOMe (**1a**), a compound that is available from CPTTO$^-$NBu$_4^+$ (not shown) and methyl tosylate in anhydrous DMF,[17] repeatedly furnished crystals of insufficient quality for structure determination by single-crystal X-ray diffraction. Similar efforts were successful for thiazolethione **1b**[5] but so far not for *N*-alkenoxy derivatives **1c**,**d**. The conformity of distances (Table 1, Entries 1–5) and angles (Table 1, Entries 6–10) determined for the heterocyclic core and the thiohydroxamate functionality of the new structure (Figure 2; Table 1, Entries 11–17) in comparison to the values obtained from earlier solid-state studies[2,14,18] allowed the diagnostic mean values, including standard deviations, to be calculated, which would allow a reasonable description of the major structural aspects of this product class (Table 1). Except for the distances within the thiohydroxamate functionality, none of these parameters deserved a comment. Bond lengths N3–C2 and C2–S2 (Table 1, Entries 2 and 11) were found to be close to mean values determined for thioamides and thioureas, thus pointing to a similar degree of electron delocalization within the these entities [C_{sp^2}=S 1.68 ± 0.02 Å, S=C_{sp^2}–N 1.35 ± 0.02 Å].[19] Transfer of electron density from nitrogen toward the C=S group, in turn, is considered to explain a slight decrease in the averaged O1–N3 distance [1.38 ± 0.01 Å] below the reference value for hydroxylamines having planarized N [1.40 ± 0.01 Å].[19]

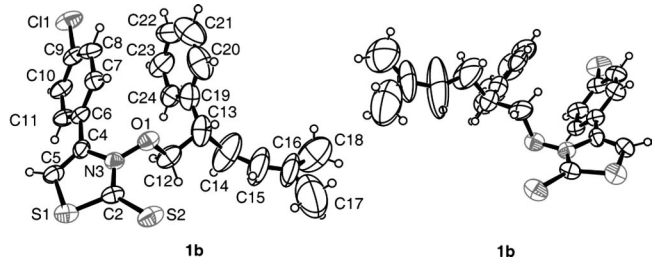


Figure 2. Projections of thiazolethione **1b** displaying least obscured view (left) and distal arrangement of thiazolethione substituents (right) (ellipsoids are drawn at the 40% probability level; hydrogen atoms are drawn as circles of an arbitrary radius; atom numbering in the projection on the right was omitted for the sake of clarity).

A surprisingly narrow distribution was moreover found for dihedral angles that characterize major conformational aspects of CPTTORs, that is, the offset of the *O*-alkyl group from the thiohydroxamate plane (82 ± 3°) and the biphenyl-type twist between the *p*-chlorophenyl and thiazolethione entities (45 ± 3°; Table 1, Entries 19 and 20; Figure 2). Most but not all CPTTOR structures showed distal orientation of aryl and *N*-alkoxy groups (Figures 2 and 3). The offset of C12 from the thiazolethione plane was attributed to steric repulsion between the *O*-alkyl group and adjacent substituents. In view of an inherent preference of hydroxylamines to adopt gauche-arranged minima,[20] it seemed reasonable to also consider polar contributions from lone pair repulsion for explaining positioning of this entity in CPTTOR

Table 1. Selected experimental (X-ray diffraction, **1b**) and computed[22] (*distal*-**1a**) parameters of CPTTORs in comparison to averaged (± standard deviation) experimental values.[a]

Entry	Parameter [Å] or [°]	X-ray crystallography **1b**	CPTTOR[a] X-ray crystallography	B3LYP[b] *distal*-**1a**
1	S1–C2	1.703(7)	1.73 ± 0.02	1.774
2	C2–N3	1.351(9)	1.35 ± 0.02	1.375
3	N3–C4	1.405(9)	1.40 ± 0.02	1.405
4	C4–C5	1.329(9)	1.34 ± 0.02	1.356
5	C5–S1	1.730(8)	1.72 ± 0.01	1.748
6	S1–C2–N3	108.0(5)	107 ± 1	106.1
7	C2–N3–C4	118.3(7)	119 ± 1	118.7
8	N3–C4–C5	108.2(8)	110 ± 2	110.6
9	C4–C5–S1	113.9(6)	113 ± 1	112.1
10	C5–S1–C2	91.6(4)	93 ± 1	92.5
11	C2–S2	1.675(8)	1.66 ± 0.01	1.657
12	N3–O1	1.380(7)	1.38 ± 0.01	1.377
13	N3–O1–C12	110.3(6)	110 ± 2	111.5
14	C4–N3–O1	120.3(7)	121 ± 1	120.7
15	C2–N3–O1	121.3(6)	120 ± 1	120.7
16	S2–C2–N3	126.6(6)	128 ± 1	127.9
17	S1–C2–S2	125.4(5)	125 ± 1	126.0
18	N3–C4–C6	123.2(8)	124 ± 3	122.6
19	C2–N3–O1–C12	84.4(8)	82 ± 3	85.6
20	N3–C4–C6–C7	–45.6(10)	±45 ± 3	–44.5

[a] Mean value from six CPTTORs: R = 2-propyl, 1-phenylpent-4-en-1-yl, 4-phenylpent-4-en-1-yl (three independent molecules), and 5-methyl-2-phenylhex-4-en-1-yl (in **1b**).[2,14,18] [b] B3LYP/6-31+G**// B3LYP/6-31+G**.

crystal structures. In solution, torsional movement about the N3,O1 bond occurs, as is evident from variable-temperature NMR spectroscopic studies.[21]

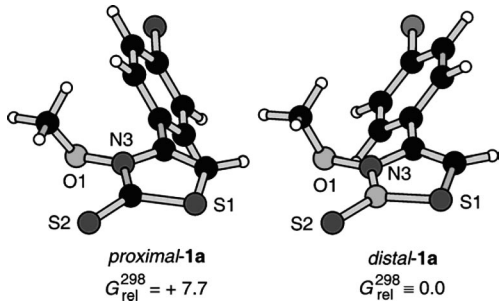


Figure 3. Ball-and-stick presentation of computed (B3LYP/6-31+G**) minima of CPTTOMe (**1a**) [see text, Supporting Information, and Table 1; relative free energies G_{rel}^{298} in kJ mol^{-1}].

In order to reduce conformational freedom associated with the *N*-alkoxy substituent, CPTTOMe (**1a**) was selected as a model for an assessment of quantum chemical methods that adequately reproduce ground-state characteristics of this product class and derived decomposition products (vide infra).[23,24] Minimum conformations of **1a** were obtained through stepwise (15°) dihedral angle variations associated with torsional movements of the *p*-chlorophenyl and the *O*-methyl substituent with respect to the thiazolethione plane by using redundant variables in minimization of energy functions. Low-energy conformations obtained from the dihedral angle scan provided input coordinates for unconstrained energy minimization. This strategy afforded two minima, one showing distal and the other proximal arrangement of substituents (Figure 3). Calculation of second derivatives (Hessian matrix) that lacked in negative eigenvalues or imaginary frequency by diagonalization, characterized computed structures as minima.

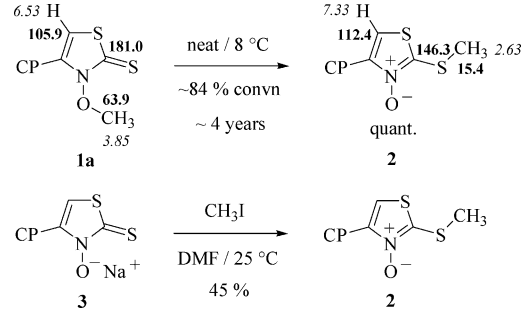
Data analysis showed that parameters found for the global minimum of CPTTOMe (**1a**) by using Becke's three parameter hybrid functional[25,26] and the 6-31+G** basis set[27–29] agreed within a precision defined by experimental mean values for this product class including standard deviations (Table 1). The only distance that diverged from the experimentally defined range related to S1–C2 (1.774 vs. 1.73 ± 0.02 Å; cf. Table 1, Entry 1). Calculations using Møller-Plesset perturbation theory second order (MP2),[30–32] reproduced some of the bond lengths slightly better (e.g., S1–C2 1.756 Å; Supporting Information). The method was less accurate for bond and torsion angles. Further investigations by using Becke's half and half functional (BHandHLYP)[33] in combination with the 6-31+G**-basis set[27–29] agreed qualitatively and quantitatively to values obtained from B3LYP theory (Supporting Information). In view of these findings, we restricted ourselves to presentation and discussion of B3LYP/6-31+G**-calculated data.

According to density functional theory, *distal*-**1a** was 7.7 kJ mol^{-1} favored by free energy (298.15 K) compared to *proximal*-**1a** (Figure 3), presumably for reasons discussed above. If correlated to findings from X-ray analysis, it is suggested that these energetic aspects furthermore serve as an explanation for statistically favoring the distal arrangement in solid-state structures.[2,14,18] Energies of rotamers having either the *O*-methyl or the *p*-chlorophenyl substituent positioned in the thiazolethione plane posed maxima as evident from negative modes of vibration (not shown).

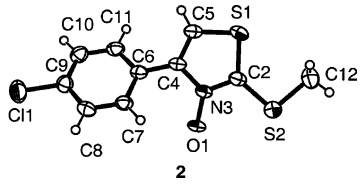
The first lesson in structural CPTTOR chemistry thus exemplified that the B3LYP/6-31+G** level of theory is able to reproduce almost all structural parameters within a precision that is defined by experimental mean values from X-ray analysis and associated standard deviations. The data furthermore suggested that conformational aspects of CPTTOR solid-state structures predominantly reflected intrinsic properties of the molecules.

Lesson 2: Isomerization

Thiazolethione **1a** was used for an extended time to pioneer the chemistry of methoxyl radical addition to norbornene.[15,17] In the course of routine ^{1}H NMR spectroscopic analysis of a previously homogeneous sample, new signals appeared, which grew in intensity at the expense of resonances from CPTTOMe (**1a**). Shifts from 3.85 to 2.63 ppm for the CH_3 resonance and from 6.53 to 7.33 ppm for 5-H pointed to changes within the heterocyclic core and the thiohydroxamate functional group (Scheme 1, top). The chemical nature of the rearrangement product, that is, 4-(*p*-chlorophenyl)-2-(methylsulfanyl)-1,3-thiazole *N*-oxide (**2**), was, for reasons of inherent difficulties to obtain analytically pure material from the mixture by chromatographic separation, clarified by independent synthesis. The crystalline residue that deposited from the reaction between CPTTO$^-$Na$^+$ (**3**) and CH_3I[34] in anhydrous DMF accounted for a yield of 45% of analytically pure *N*-oxide **2** (Scheme 1, bottom). The supernatant contained a mixture of alkylation products **1a** and **2**, which, for reasons given above, was discarded. As a result of difficulties in earlier studies to unambiguously verify the presence of the *N*-oxide oxygen atom by IR and ^{13}C NMR spectroscopy,[2,3] the identity of heterocycle **2** was verified by X-ray diffraction analysis (Figure 4).



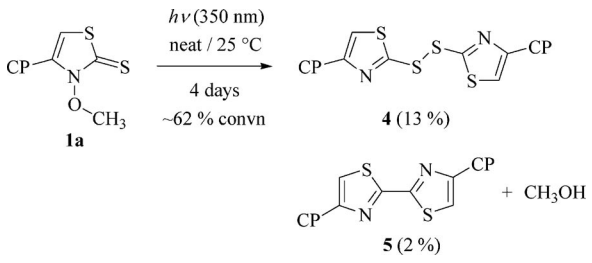
Scheme 1. Isomerization of CPTTOMe (**1a**) by methyl transfer from oxygen to sulfur (top) and independent synthesis of *N*-oxide **2** (bottom) [figures in bold refer to diagnostic ^{13}C NMR shifts data, numbers in italics to ^{1}H NMR shifts values ($CDCl_3$, 25 °C)].



2

Figure 4. Ellipsoid graphics (50% probability level) of *N*-oxide (**2**) in the solid state (hydrogen atoms are drawn as circles of an arbitrary radius).

Attempts to accelerate the conversion into **2** at elevated temperatures (80 °C) resulted in unspecific decomposition of neat CPTTOMe (**1a**). Photoactivation (350 nm, 25 °C) of solid **1a** provided disulfide **4**[11] (13% after 4 d) along with 2% of substituted bithiazyl **5**[11] and CH_3OH, without providing evidence for formation of *N*-oxide **2** (^1H and ^{13}C NMR; Scheme 2). Bithiazyl **5** is a familiar photodecomposition product of disulfide **4**.[11] The methanol balance remained unfortunately erratic, even if the reaction was conducted in a sealed tube. The current data point to the formation of ca. 0.5 equiv. of CH_3OH per decomposed molecule of CPTTOMe (**1a**), which is under further investigation.



Scheme 2. Products formed from photochemical decomposition of neat CPTTOMe (**1a**).

Endocyclic bond lengths in the crystal structure of *N*-oxide **2** (Table 2, Entries 1–10) were similar to those of substituted thiazoles.[35–38] Values of ca. 112° for bond angles at C2 and N3 differed from respective parameters in thiazolethiones (Table 2, Entries 6 and 7). A close contact between *N*-oxide and methylsulfanyl entities [O1···S2 2.880(3) Å], and the magnitude of bond angles at C2 (S1–C2–S2 > S2–C2–N3) and N3 (O1–N3–C4 > C2–N3–O1) pointed to $n_O \rightarrow \sigma^*_{C,S}$ attraction, similar to interactions observed in 2-alkylsulfanylpyridine *N*-oxides.[19,39]

The computed (B3LYP/6-31+G**) global minimum of *N*-oxide **2** showed a gauche arrangement of the N3–C2–S2–C12 segment (58.5°; i.e., *gauche*-**2**). This conformation was favored by ΔG^{298} = 6.3 kJ mol^{-1} (gas phase) to an antiperiplanar positioning of the N3–C2–S2–C12 entity (*anti*-**2**). The latter arrangement was found in the crystal structure of **2**. Important structural aspects, for instance the O1···S2 distance (2.872 Å) that fell short of the sum of associated van der Waals radii (3.32 Å)[40] and bond angles describing the *N*-oxide bent toward the methylsulfanyl group in *anti*-**2**, were precisely reproduced by theory (Table 2, Entries 13–16).

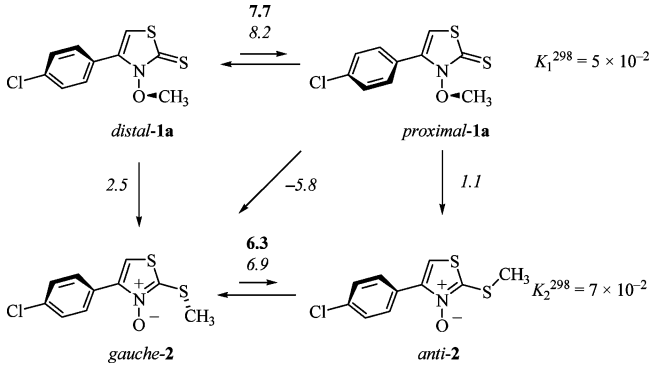
Table 2. Selected experimental (X-ray diffraction) and computed[22] parameters of *N*-oxide **2** (cf. Schemes 1 and 2).

Entry	Parameter [Å] or [°]	X-ray crystallography **2**	B3LYP[a] *anti*-**2**[b]
1	S1–C2	1.710(2)	1.737
2	C2–N3	1.331(3)	1.342
3	N3–C4	1.409(3)	1.420
4	C4–C5	1.348(3)	1.363
5	C5–S1	1.704(2)	1.738
6	S1–C2–N3	112.3(2)	112.4
7	C2–N3–C4	113.5(2)	113.6
8	N3–C4–C5	110.6(2)	111.4
9	C4–C5–S1	113.5(2)	112.7
10	C5–S1–C2	90.0(1)	89.9
11	C2–S2	1.722(2)	1.745
12	N3–O1	1.311(2)	1.295
13	C4–N3–O1	124.5(2)	124.7
14	C2–N3–O1	122.0(2)	121.6
15	S2–C2–N3	118.6(2)	117.9
16	S1–C2–S2	129.0(1)	129.7
17	N3–C4–C6	121.9(2)	121.6
18	N3–C4–C6–C7	33.5(3)	32.5
19	N3–C2–S2–C12	–178.8(2)	–179.5

[a] B3LYP/6-31+G**//B3LYP/6-31+G**. [b] Antiperiplanar arrangement of segment N–C–S–C in **2** (for *gauche*-**2** refer to Scheme 3; for data and computed structure of *gauche*-**2** see the Supporting Information).

According to theory, rearrangement of CPTTOMe (**1a**) into *N*-oxide **2** was predicted to be endothermic by 2.5 kJ mol^{-1} (Scheme 3). If the methyl transfer occurred from the higher energy rotamer having the *N*-methoxy and the *p*-chlorophenyl group located in proximal position, the rearrangement became weakly exothermic ($\Delta_R H$ = –5.8 kJ mol^{-1}, Scheme 3). Calculated energy differences between isomers **1a** and **2**, and those for the respective isomerization of *N*-methoxy-4-methyl-1,3-thiazole-2(3*H*)-thione into 2-methylsulfanyl-4-methyl-1,3-thiazole *N*-oxide ($\Delta_R H$ = –0.3 kJ mol^{-1}, Supporting Information) were small and pointed to a marked stability of the cross-conjugated π-electron system in thiazolethiones.[3] It is worth mentioning that the *N*-(methoxy)pyridine-2(1*H*)-thione to 2-methylsulfanylpyridine *N*-oxide rearrangement according to theory was predicted to be notably exothermic ($\Delta_R H$ = –30.5 kJ mol^{-1}, Supporting Information). This result was in accord with the observation that alkyl shifts in pyridine-derived cyclic *O*-alkyl thiohydroxamates are fairly common reactions. Isomerizations of this kind generally occur quantitatively to furnish 2-alkylpyridine *N*-oxides from neat *N*-(alkoxy)pyridine-2(1*H*)-thiones within ca. 14 h at ca. 5 °C, in particular for *N*-benzyloxy derivatives having at least one electron-releasing group attached to the aromatic substituent.[16,41,42] Because data for distinguishing kinetic order of reactants in *O*-alkyl thiohydroxamate to *S*-alkylthiohydroximate rearrangements were not available from the literature, it was refrained from extending the computational analysis beyond this point.[43,44]

In summary, the second lesson demonstrated that solid CPTTOMe (**1a**) selectively isomerized through methyl transfer from thiohydroxamate O to thione S. The reaction

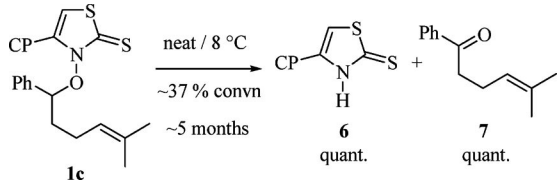


Scheme 3. Energetics associated with (i) conformational changes in thiazole derivatives **1a** and **2**, and (ii) isomerization **1a**→**2** [B3LYP/6-31+G**; figures in italics refer to reaction enthalpies (in kJ mol^{-1}, zero-point vibrational energy corrected, 0 K), numbers in bold describe computed free-energy changes (kJ mol^{-1}, 298.15 K)].

was slow and according to theory weakly endothermic. The reverse reaction **2** → **1a** and further examples of alkyl migration, for example, of primary or secondary substituents, have so far not been observed. Although the mechanism of the rearrangement remains unknown, the fact that the small methyl group in **1a** and not the secondary benzyl group in **1c** migrated seemed to favor nucleophilic to homolytic substitution (cf. Lesson 4).

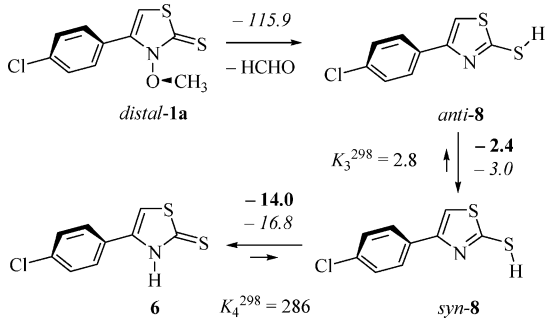
Lesson 3: Fragmentation

Thiazolethione **1c** served as a key reagent for developing a free radical version of bromo- and iodocyclization.[5,45] While working with the compound, its propensity to undergo fragmentation was noted (Scheme 4). A neat sample that, for instance, was stored for 5 months at –18 °C provided 37% each of thiazolethione **6** and **7**. The residual material accounted for thione **1c**. Products of *O*-alkylthiohydroxamate to *S*-alkylthiohydroximate rearrangement, that is, the reaction *N*-(5-methyl-1-phenylhex-4-ene-1-oxy)-pyridine-2(1*H*)-thione would quantitatively undergo,[16,39] were not observed.



Scheme 4. Fragmentation of thiazolethione **1c**.

Theory stated that fragmentation of CPTTOMe (**1a**) into formaldehyde and thiazolethione **6** poses a strongly exothermic reaction (Scheme 5). For thermochemical reasons, thiazolethiol **8** is expected to be formed in the initial step, with rotamer *anti*-**8** being slightly higher in energy than *syn*-**8** (Scheme 5). The latter compound is predicted to be 16.8 kJ mol^{-1} higher in free energy than its thione tautomer **6**. The associated equilibrium constant (K_4^{298} = 286, gas phase) probably shows strong media effects similar to those reported for the 2-mercaptopyridine/pyridine-2(1*H*)-thione equilibrium.[46]



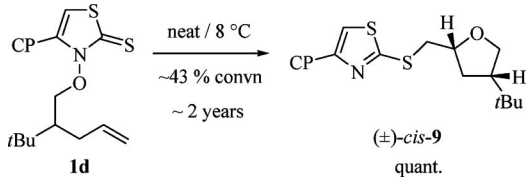
Scheme 5. Thermochemistry of (i) CPTTOMe fragmentation and (ii) thiolactim/thiolactam equilibrium [B3LYP/6-31+G**; figures in italics refer to reaction enthalpies (kJ mol^{-1}, zero-point vibrational energy corrected, 0 K), numbers in bold describe computed free-energy changes (kJ mol^{-1}, 298.15 K); the *syn*/*anti* notation refers to arrangement of segment N–C–S–H].

Thiazole-2(3*H*)-thiones form H-atom bridged thiolactam dimers in the solid state.[51] In solution ($CDCl_3$), the 5-H resonance from the heterocyclic core of **3** (δ =7.18 ppm) differed to some extent from chemical shifts reported for this site in alkylsulfanylthiazole *cis*-**9** (δ =7.32 ppm, vide infra) and derivatives thereof (7.44–7.55 ppm).[36–38]

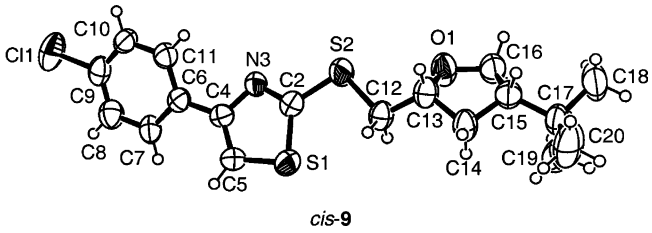
To summarize, the third lesson taught that thiazolethione **1c** underwent fragmentation through formal 1,5-H-atom shift. It remained unclear whether the reaction proceeded via radical or polar intermediates. Alternative CPTTOR decomposition products were not observed. Apart from **1c**, none of the structurally related CPTTOR explored in our studies, that is, neat samples of 4-(*p*-chlorophenyl)-*N*-(1-phenyl-1-ethoxy)- and 4-(*p*-chlorophenyl)-*N*-(1-phenylpent-4-en-1-oxy)-1,3-thiazole-2(3*H*)-thione (not shown) exhibited similar reactivity. The latter two compounds were stable, if stored as neat samples for 5 years at ca. 5 °C.[47]

Lesson 4: Rearrangement

Thiazolethione **1d** played a major role in the development of a model for predicting stereoselectivity in alkenoxyl radical 5-*exo*-trig cyclizations.[8] In routine analysis, significant amounts of thiazole *cis*-**9** (Scheme 6, Figure 5) were identified in a sample of previously homogeneous thione **1d**, which was kept for ca. 2 years at 8 °C in the dark.



Scheme 6. Rearrangement of thiazolethione **1d**.



cis-**9**

Figure 5. Ellipsoid graphics (50% probability level) of thiazole *cis*-**9** in the solid state (one enantiomer from the racemate was arbitrarily selected for presentation; hydrogen atoms are depicted as circles of an arbitrary radius).

Heterocycle *cis*-**9** crystallized in the centrosymmetric space group $P2_1/c$, thus pointing to formation of its racemate. Bond lengths and angles of the heterocyclic core were within the experimental error similar to parameters determined for 1,3-thiazole through microwave spectroscopy.[35] Shortening of the N3–C2 distance, a more acute endocyclic angle at N3, and a widening of S1–C2–N3 distinguished the 1,3-thiazole entity in *cis*-**9** from the thiazolethione nucleus[48–51] (Tables 1, 2, and 3, Entries 2, 6, 7).[2,14] The alkylsulfanyl side chain showed antiperiplanar arrangement with respect to the N3–C2–S2–C12 unit [180.0(4)°].

Table 3. Selected experimental (X-ray diffraction) and computed[22] parameters of thiazole *cis*-**9** and 2-thiazolethiol *anti*-**8** (cf. Figure 5, Schemes 4 and 5).

Entry	Parameter [Å] or [°]	X-ray crystallography *cis*-**9**	B3LYP[a] *anti*-**8**
1	S1–C2	1.731(4)	1.762
2	C2–N3	1.307(4)	1.296
3	N3–C4	1.398(4)	1.387
4	C4–C5	1.344(5)	1.373
5	C5–S1	1.722(4)	1.735
6	S1–C2–N3	115.2(3)	114.6
7	C2–N3–C4	109.7(3)	111.9
8	N3–C4–C5	115.6(3)	114.4
9	C4–C5–S1	110.6(3)	110.8
10	C5–S1–C2	88.9(2)	88.4
11	C2–S2	1.733(4)	1.769
15	S2–C2–N3	120.4(3)	121.1
16	S1–C2–S2	124.4(2)	124.3
17	N3–C4–C6	118.4(3)	118.9
18	N3–C4–C6–C7	159.2(3)	9.0
19	N3–C2–S2–R[b]	178.7(3)	176.9

[a] B3LYP/6-31+G**//B3LYP/6-31+G**. [b] R = C_{12} in *cis*-**9** and H in *anti*-**8**.

The observed selectivity for the solid state reaction **1d** → *cis*-**9** is similar but not identical to the 2-*tert*-butylpent-4-en-1-oxyl radical ring closure in solution, which occurs with 90:10 *cis*/*trans* diastereoselectivity (25 °C).[8] Extension of this interpretation to the formation of *cis*-**9** would require N,O-homolysis to occur in the initial step. The computed dissociation energy for the N,O bond in *N*-methoxy-4-methylthiazole-2(3*H*)-thione is ca. 160 kJ mol^{-1},[52] which underlines the inherent weakness of this connectivity in *O*-alkyl thiohydroxamates. Homolysis of this entity may be followed by radical cyclization and combination in the solid state, with the low temperature and possibly the crystal lattice contributing to improved diastereoselectivity.

In summary, the fourth lesson of structural CPTTOR chemistry exemplified that thiazolethione **1d** rearranged in the solid state, without being photoactivated or subjected to higher temperatures (ca. 80 °C).

Concluding Remarks

CPTTORs originally were designed to solve the long-standing problem of alkoxyl radical generation under mild conditions from sources that are easy to prepare and handle. A decade of experience with this product class shows that the major aims in this sense have been fulfilled. Longer term projects now have uncovered that at least three modes of CPTTOR decomposition exist, which are distinctively different from homolytic substitutions in radical chain reactions.

Two out of three pathways reflected the inherent weakness of the N,O bond, which, after all, is the *conditio sine qua non* for the product class to serve as selective oxyl radical precursor. The third mode of decomposition furnished 4-(*p*-chlorophenyl)-2-methylsulfanyl-1,3-thiazole *N*-oxide through methyl translocation from oxygen to sulfur. None of the reactions, however, provides a potent inhibitor for radical chain reactions.

The newly discovered pathways occurred in neat solid CPTTOR samples selectively, within detection limits (NMR) even specifically. The examples so far are limited by number. From the available data it seems that structural prerequisites exist for the reactions to become relevant and to occur in a specific manner. In solution, if not applied for the purpose they were designed for, the compounds and structurally related 3-alkoxy derivatives thereof, decompose at more or less the same rate, leading to a diversity of thiazole derivatives, carbonyl compounds, and alkoxyl radical derived products.[7] This observation suggests that the key for the observed specificity resides in CPTTOR crystal lattices. A systematic pursuit of solid state chemistry, however, requires knowledge about crystal structures of those CPTTORs that underwent the reactions outlined above. Although this information was not available by the time the study was performed, it has the potential to open a new chapter of CPTTOR chemistry.

Experimental Section

General Remarks: For spectroscopic equipment, preparation of *N*-alkoxythiazolethiones **1a**–**d**, general laboratory practice, and instrumentation see ref.[8] and the Supporting Information.

4-(4-Chlorophenyl)-3-[(5-methyl-2-phenylhex-4-enyl)oxy]-1,3-thiazole-2(3H)-thione (1b):[5] Crystals suitable for X-ray diffraction were grown by slowly allowing petroleum ether to diffuse into a saturated solution of **1b** in CH_2Cl_2. $C_{22}H_{22}ClNOS_2$ (415.98), T = 301(2) K, λ = 0.71093 Å, monoclinic, $P2_1/c$, a = 18.993(8) Å, b = 6.313(2) Å, c = 18.241(7) Å, β = 95.52(5)°, Z = 4, μ = 0.379 mm^{-1},

completeness to 2θ = 99.6%, goodness-of-fit on F^2 = 0.862, final *R* indices [$I>2\sigma(I)$]: R_1 = 0.0714, wR_2 = 0.1571.

4-(4-Chlorophenyl)-2-(methylsulfanyl)-1,3-thiazole-*N*-Oxide (2): A solution of 4-(*p*-chlorophenyl)-*N*-hydroxy-1,3-thiazole-2(3*H*)-thione (1.22 g, 5.00 mmol) in MeOH (25 mL) was treated with NaOH (200 mg, 5.00 mmol) and stirred for 1 h at 25 °C in the dark. The solvent was removed under reduced pressure (200→20 mbar, 40 °C). The residue was freeze dried to furnish 4-(4-chlorophenyl)-3-hydroxy-1,3-thiazole-2(3*H*)-thione sodium salt **3** as a tan powder. The sodium salt was dissolved in anhydrous DMF (25 mL) and treated with CH_3I (710 mg, 5.00 mmol). The reaction mixture was stirred for 4 d in the dark. The crop of colorless crystals that deposited from the solution was collected by filtration, washed (Et_2O), and dried (580 mg, 45%). M.p. 188–190 °C. R_f = 0.02 (SiO_2; pentane/Et_2O, 1:1). UV/Vis (MeOH): λ ($\log\varepsilon$) = 255 (3.41) nm. IR (KBr): $\tilde{\nu}$ = 3128 (m), 1482 (m), 1429 (w), 1388 (s), 1327 (w), 1287 (s), 1231 (s), 1092 (s), 1022 (m), 977 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.63 (s, 3 H, SCH_3), 7.33 (s, 1 H, 5-H), 7.41 (d, J = 11.2 Hz, 2 H, Ar-H), 7.91 (d, J = 11.2 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4 (SCH_3), 112.4 (5-C), 127.5, 129.1, 129.2, 129.8, 136.3 (Ar-C), 146.3 (2-C) ppm. MS (70 eV, EI): *m*/*z* (%) = 257/259 (37/16), 240/242 (100/45), 168/170 (20/8), 159 (7), 136 /138 (21/9), 117 (85), 103 (20). $C_{10}H_8ClNOS_2$ (257.75): calcd. C 46.70, H 3.14, N 5.45, S 24.88; found C 46.52, H 3.28, N 5.47, S 24.96. Crystals suitable for X-ray diffraction were grown from a saturated solution in MeOH. T = 294(2) K, λ = 0.71073 Å, monoclinic, $P2_1/n$, a = 7.247(1) Å, b = 6.317(1) Å, c = 24.003(5) Å, β = 93.10(3)°, Z = 4, μ = 0.698 mm^{-1}, completeness to 2θ = 94.9%, goodness-of-fit on F^2 = 1.093, final *R* indices [$I>2\sigma(I)$]: R_1 = 0.0278, wR_2 = 0.0710.

4-(4-Chlorophenyl)-1,3-thiazole-2(3*H*)-thione (6): A sample of analytically pure **1c** was stored for ca. 5 months in a refrigerator (8 °C) to furnish a mixture of 37% **6**, an equivalent amount of **7** and 73% of **1c** (^1H NMR). The mixture was purified by chromatography (SiO_2; petroleum ether/Et_2O, 2:1; R_f = 0.25) to furnish thione **6** as pale-yellow prisms. M.p. 207–210 °C. ^1H NMR (250 MHz, [D_6]-acetone): δ = 7.18 (s, 1 H, 5-H), 7.53 (m, 2 H, Ar-H), 7.83 (m, 2 H, Ar-H) ppm. MS (70 eV, EI): *m*/*z* (%) = 227 (100) [M^+], 168 (50), 133 (49), 89 (35). HRMS: calcd. 226.9628; found 226.9629. $C_9H_6ClNS_2$ (227.73): calcd. C 47.58, H 2.66, N 6.17, S 28.17; found C 47.69, H 2.81, N 6.36, S 28.48.

***cis*-4-(4-Chlorophenyl)-2-{[(4-methyltetrahydrofuran-2-yl)methyl]-thio}-1,3-thiazole [*cis*-(9)]:** A sample of analytically pure thiazolethione **1d** was kept for 2 years in a refrigerator (8 °C). Purification of the sample by chromatography [SiO_2; petroleum ether/*tert*-butyl methyl ether, 9:1; R_f = 0.75] furnished thiazole *cis*-**9** as a colorless crystalline solid. M.p. 69–71 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.90 (s, 9 H, *t*Bu), 1.50 (m_c, 1 H, 3′-H), 2.06 (ddd, J = 13.1, 7.6, 5.5 Hz, 1 H, 3′-H), 2.14–2.29 (m, 1 H, 4′-H), 3.42–3.52 (m, 2 H, 6′-H), 3.69 (t, J = 8.5 Hz, 1 H, 5′-H), 3.84 (t, J = 8.2 Hz, 1 H, 5′-H), 4.26 (dq, J_d = 9.5 Hz, J_q = 5.8 Hz, 1 H, 2′-H), 7.32 (s, 1 H, 5-H), 7.34–7.40 (m, 2 H, Ar-H), 7.78–7.84 (m, 2 H, Ar-H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 28.0 (CH_3), 31.7 [C-(CH_3)$_3$], 33.9 (3′-C), 39.5 (4′-C), 51.2 (6′-C), 69.9 (5′-C), 78.6 (2′-C), 108.3 (5-C), 113.0, 127.9 (Ar-C), 129.3 (Ar-C), 132.9, 134.3, 154.2 (2-C) ppm. MS (70 eV, EI): *m*/*z* (%) = 173 (11), 91 (35), 70 (100), 57 (54). $C_{18}H_{22}ClNOS_2$ (367.95): calcd. C 58.76, H 6.03, N 3.81, S 17.43; found C 59.11, H 5.99, N 3.51, S 17.45. Crystals suitable for X-ray diffraction were grown by slowly allowing petroleum ether to diffuse into a saturated solution of *cis*-**9** in Et_2O. T = 299(2) K, λ = 0.71093 Å, monoclinic, $P2_1/c$, a = 15.3874(6) Å, b = 9.8914(4) Å, c = 12.3641 (6) Å, β = 90.837 (4)°, Z = 4, μ = 0.428 mm^{-1}, completeness to 2θ = 99.7%, goodness-of-fit on F^2 = 0.991, final *R* indices [$I > 2\sigma(I)$]: R_1 = 0.0540, wR_2 = 0.1439.

Photochemical Decomposition of 4-(4-Chlorophenyl)-3-methoxy-1,3-thiazole-2(3*H*)-thione (1a): Thiazolethione **1a** (100 mg, 0.39 mmol) was irradiated in a closed reaction vessel using a Rayonet photoreactor (350 nm, 25 °C) for 4 d. $CDCl_3$ was added through the stopcock, and the resulting solution was analyzed by NMR spectroscopy for qualitative and quantitative product analysis. The solvent was afterwards removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; petroleum ether/CH_2Cl_2, 1:1; R_f = 0.31) to afford a colorless solid that consisted of as 93:7 mixture of compounds **4** and **5**. Analysis for **4/5** (93:7): calcd. C 48.16, H 2.25, N 6.24; found C 47.51, H 2.24, N 6.16. Data for 2,2′-bis[4-(*p*-chlorophenyl)thiazyl]disulfide (**4**): Yield: 13%. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.38 (m, 4 H, Ar-H), 7.50 (s, 2 H, 5-H), 7.80 (m, 4 H, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 116.0 (5-C), 127.5 (Ar-C), 128.9 (Ar-C), 132.0 (Ar-C), 134.3 (Ar-C), 155.9 (4-C), 165.0 (2-C) ppm. Data for 2,2′-bis[4-(*p*-chlorophenyl)thiazyl] (**5**): Yield: 2%. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.34 (m, 4 H, Ar-H), 7.44 (s, 2 H, 5-H), 7.72 (m, 4 H, Ar-H) ppm.

CCDC-699514 (for **1a**), -699515 (for *cis*-**9**), and -699516 (for **2**) 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.

Supporting Information (see footnote on the first page of this article): Instrumentation, calculated energies (BHandHLYP/6-31+G**), Gaussian archives and atomic coordinates of computed structures (B3LYP, BHandHLYP, MP2); computational data on *N*-methoxy-4-methyl-1,3-thiazole-2(3*H*)-thione to 2-methylsulfanyl-4-methylthiazole *N*-oxide and *N*-methoxypyridine-2(1*H*)-thione to 2-methylsulfanylpyridine *N*-oxide rearrangements.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 690: Elektronendichte – Theorie und Experiment).

[1] J. Hartung, M. Schwarz, *Synlett* **1997**, 848–850; J. Hartung, M. Schwarz, *Synlett* **1997**, 1116.
[2] J. Hartung, M. Schwarz, I. Svoboda, H. Fuess, M.-T. Duarte, *Eur. J. Org. Chem.* **1999**, 1275–1290.
[3] J. Hartung, *Eur. J. Org. Chem.* **2001**, 619–632.
[4] J. Hartung, R. Kneuer, M. Schwarz, I. Svoboda, H. Fuess, *Eur. J. Org. Chem.* **1999**, 97–106.
[5] J. Hartung, R. Kneuer, S. Laug, P. Schmidt, K. Špehar, I. Svoboda, H. Fuess, *Eur. J. Org. Chem.* **2003**, 4033–4052.
[6] J. Hartung, M. Schwarz, *Org. Synth., Coll. Vol.* **2004**, *10*, 437–441.
[7] J. Hartung, K. Daniel, T. Gottwald, A. Groß, N. Schneiders, *Org. Biomol. Chem.* **2006**, *4*, 2313–2322.
[8] J. Hartung, K. Daniel, C. Rummey, G. Bringmann, *Org. Biomol. Chem.* **2006**, *4*, 4089–4100.
[9] U. Wille, C. Jargstorff, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1036–1041.
[10] R. Krähmer, L. Henning, M. Findeisen, D. Müller, P. Welzel, *Tetrahedron* **1998**, *54*, 10753–10760.
[11] W. Adam, J. Hartung, H. Okamoto, C. R. Saha-Möller, K. Špehar, *Photochem. Photobiol.* **2000**, *72*, 619–624.
[12] J. Hartung in *Encyclopedia of Reagents in Organic Chemistry* (Ed.: D. Crich), John Wiley & Sons, Chichester, **2008**, pp. 175–179.

[13] J. Hartung, T. Gottwald, K. Špehar, *Synthesis* **2002**, 1469–1498.
[14] J. Hartung, M. Schwarz, E. F. Paulus, I. Svoboda, H. Fuess, *Acta Crystallogr., Sect. C* **2006**, *62*, o386–o388.
[15] J. Hartung, N. Schneiders, T. Gottwald, *Tetrahedron Lett.* **2007**, *48*, 6327–6330.
[16] J. Hartung, M. Hiller, P. Schmidt, *Liebigs Ann.* **1996**, 1425–1436.
[17] J. Hartung, K. Špehar, I. Svoboda, H. Fuess, M. Arnone, B. Engels, *Eur. J. Org. Chem.* **2005**, 869–881.
[18] J. Hartung, J. Bachmann, I. Svoboda, H. Fuess, *Acta Crystallogr., Sect. E* **2008**, *64*, m299.
[19] F. H. Allen, O. Kennard, D. G. Waston, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1987**, S1–S19.
[20] M. Raban, D. Kost, *Tetrahedron* **1984**, *40*, 3345–3381.
[21] J. Hartung, R. Kneuer, M. Schwarz, M. Heubes, *Eur. J. Org. Chem.* **2001**, 4733–4736.
[22] Quantum chemical calculations were carried out on Intel LinuX workstations: M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. G. Rega, A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03* (Revision C.01), Gaussian, Inc., Wallingford, CT, **2004**.
[23] F. Jensen, *Introduction to Computational Chemistry*, Wiley, Chichester, **1999**.
[24] R. Kakkar, A. Dua, S. Zaidi, *Org. Biomol. Chem.* **2007**, *5*, 547–557.
[25] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.
[26] C. T. Lee, W. T. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.
[27] R. Ditchfield, W. J. Hehre, J. A. Pople, *J. Chem. Phys.* **1971**, *54*, 724–728.
[28] W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257–2261.
[29] P. C. Hariharan, J. A. Pople, *Mol. Phys.* **1974**, *27*, 209–214.
[30] C. Møller, M. S. Plesset, *Phys. Rev.* **1934**, *46*, 618–622.
[31] M. J. Frisch, M. Head-Gordon, J. A. Pople, *Chem. Phys. Lett.* **1990**, *166*, 281–289.
[32] M. Head-Gordon, T. Head-Gordon, *Chem. Phys. Lett.* **1994**, *220*, 122–128.
[33] A. D. Becke, *Phys. Rev.* **1988**, *A38*, 3098–3100.
[34] D. H. R. Barton, D. Crich, G. Kretschmar, *J. Chem. Soc. Perkin Trans. 1* **1986**, 39–53.
[35] L. Nygaard, E. Asmussen, J. H. Høg, R. C. Maheshwari, C. H. Nielsen, I. B. Petersen, J. Rastrup-Andersen, G. O. Sørensen, *J. Mol. Struct.* **1971**, *8*, 225–233.
[36] J. Hartung, K. Daniel, P. Schmidt, S. Laug, I. Svoboda, H. Fuess, *Acta Crystallogr., Sect. E* **2005**, *61*, o3974–o3976.
[37] J. Hartung, K. Daniel, P. Schmidt, S. Laug, I. Svoboda, H. Fuess, *Acta Crystallogr., Sect. E* **2005**, *61*, o3971–o3973.
[38] J. Hartung, P. Schmidt, I. Svoboda, H. Fuess, *Acta Crystallogr., Sect. E* **2005**, *61*, o1736–o1737.
[39] J. Hartung, I. Svoboda, H. Fuess, *Acta Crystallogr., Sect. C* **1996**, *52*, 2841–2844.
[40] A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441–452.
[41] B. P. Hay, A. L. J. Beckwith, *J. Org. Chem.* **1988**, *53*, 4330–4334.
[42] J. Hartung, M. Hiller, P. Schmidt, *Chem. Eur. J.* **1996**, *2*, 1014–1023.
[43] U. Schöllkopf, I. Hoppe, *Justus Liebigs Ann. Chem.* **1972**, *765*, 153–170.
[44] S. Wolfe, K. Yang, N. Weinberg, Z. Shi, Y.-H. Hsieh, R. D. Sharma, S. Ro, C.-K. Kim, *Chem. Eur. J.* **1998**, *4*, 886–902.
[45] J. Hartung, T. M. Kopf, R. Kneuer, P. Schmidt, *C. R. Acad. Sci. Paris, Chimie/Chemistry* **2001**, 649–666.
[46] D. Moran, K. I. Sukcharoenphon, R. Puchta, H. F. Schaefer III, P. v. R. Schleyer, C. D. Hoff, *J. Org. Chem.* **2002**, *67*, 9061–9069.
[47] M. Schwarz, PhD Thesis, Universität Würzburg, **2000**.
[48] M. D. Estrada, A. López-Castro, *Acta Crystallogr., Sect. C* **1989**, *45*, 1977–1979.
[49] G. Pèpe, M. Pierrot, *Acta Crystallogr., Sect. B* **1976**, *32*, 1321–1325.
[50] G. Pèpe, M. Pierrot, *Acta Crystallogr., Sect. B* **1976**, *32*, 1317–1320.
[51] J. Hartung, K. Daniel, I. Svoboda, H. Fuess, *Acta Crystallogr., Sect. E* **2005**, *61*, o1744–o1746.
[52] M. Arnone, J. Hartung, B. Engels, *J. Phys. Chem. B* **2005**, *109*, 5943–5950.

Received: January 22, 2009
Published Online: July 9, 2009

