the fact that the substituted phenyl group in our nitroxide radical is much closer to the N π orbital, increasing the inductive interaction. This result agrees with the report of Janzen[40] that the phenyl ring tends to line up with the nitroxyl p-π orbital.

Acknowledgment. T.-I.H. expresses his gratitude for encouragement and helpful discussions with Professors H. Hatano, A. Naito, and S. Okazaki and Dr. K. Nozaki at Kyoto University. Helpful suggestions from Professor A. J. Swallow are also gratefully acknowledged. Financial support from the National Science Council of R. O. C. (Taiwan) is acknowledged (NSC80-0208-M002-38).

Registry No. 1, 1694-19-5; 2, 1657-50-7; 3, 13041-70-8; 5, 15638-14-9; 6, 37163-82-9; 7, 18869-29-9; 8, 103-30-0; 9, 1657-56-3; 10, 18869-30-2; 11, 134735-76-5; 27 (X = OMe), 134735-77-6; 27 (X = *i*-Pr), 134735-78-7; 27 (X = Me), 134735-79-8; 27 (X = H), 21894-25-7; 27 (X = Cl), 134735-80-1; 27 (X = Br), 134735-81-2; 27 (X = CN), 134735-82-3; TEA, 121-44-8; DIPEA, 7087-68-5; DIPMA, 10342-97-9; PBN, 3376-24-7; benzylmagnesium bromide, 1589-82-8.

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Reactivity of the Thiazolium C2 Ylide in Aprotic Solvents: Novel Experimental Evidence for Addition Rather Than Insertion Reactivity

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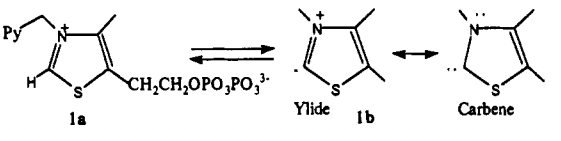
Two thiazolium compounds were synthesized specifically labeled at their C2 positions: 3,4,5-trimethyl[2-^{13}C]thiazolium nitrate and 3-benzyl-5-(β-ethoxyethyl)-4-methyl[2-^{13}C]thiazolium bromide, with a view to examine their pathways leading to dimerization in strongly basic medium using ^{13}C NMR. On addition of less than 1 equiv of base the *N*-methyl ion first formed an unsymmetrical dimer in which the C2 atoms of two molecules were bonded to each other and only one of them still carried a hydrogen; that unsymmetrical dimer upon addition of excess base lost the remaining hydrogen at C2 and was converted to a mixture of syn and anti symmetrical dimers in nearly equal amounts. The sequence of observations on addition of base to the *N*-methyl derivative is consistent with nucleophilic addition of the conjugate base to a second thiazolium ion at its C2 position. Since the unsymmetrical dimer is formed first, rather than the symmetrical dimer, the latter cannot result from direct dimerization of two conjugate bases (ylides) by a carbene mechanism. Instead, a carbanion-addition mechanism was further supported by two experiments. A "crossover" experiment was designed in which unsymmetrical dimers were detected in Me_2SO on addition of limiting potassium *tert*-butoxide to thiazolium ions containing [2-^{13}C]-H and [2-^{12}C]-D, under conditions such that there was little H/D exchange observed at the C2 position. Also, *N*-3-alkenylthiazolium ions were synthesized, that, if carbenic reactivity had existed, would have resulted in formation of cyclopropanes. In preference to the intramolecular reaction, intermolecular unsymmetrical dimers resulted in each case, consistent with nucleophilic addition. On addition of base to the *N*-benzylthiazolium ion, the first product to be detected by ^{13}C NMR was the syn/anti symmetrical dimer mixture (again bonded via the C2 atoms), that underwent a [1,3]-sigmatropic rearrangement of one of the benzyl groups from N3 to C2. According to ^{1}H NMR recorded within minutes of mixing, the unsymmetrical dimer precedes the symmetrical one for this salt as well. The reactivity of the C2 ylide derived from the *N*-methyl and *N*-benzylthiazolium ions can be rationalized according to an ionic addition reaction, implying that the related thiamin (vitamin B_1) conjugate base (ylide) behaves similarly.

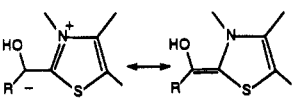
Introduction

The chemistry of thiamin diphosphate (**1a**) dependent enzymes is governed by the very unusual properties of two highly conjugated chemical structures: the ylide **1b**, obtained by deprotonation of the thiazolium ring at C2, and the C2α carbanion (or enamine, **2**) obtained upon decarboxylation of the most prevalent substrate for such enzymes, i.e. α-keto acids.[1] In recent years, we reported quantitative generation of enamines **2** from the corresponding 2-alkyl- and 2-benzylthiazolium salts in aprotic solvents by the addition of nonnucleophilic bases so as to avoid nucleophilic addition, and subsequent ring opening at C2.[2] The pK_a's at the C2α position were recently determined in Me_2SO for a number of 2-alkyl- and 2-benzylthiazolium salts,[3] indicating that in Me_2SO that



(1)

Py= 5- (4-amino-2-methyl)pyrimidinyl



2

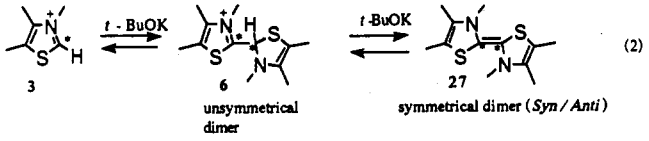
position possesses stronger thermodynamic acidity than hitherto assumed. In addition, the facile electrochemical one-electron oxidation of the enamines was also reported.[4] In recent reports the pK_a for ylide generation in water was revised upward from its previous value of 12.7 determined

(1) Kluger, R. *Chem. Rev.* **1987**, *87*, 863–876 for a recent review.
(2) (a) Jordan, F.; Kudzin, Z. H.; Rios, C. B. *J. Am. Chem. Soc.* **1987**, *109*, 4415–4416. (b) Jordan, F.; Kudzin, Z. H.; Rios, C. B. *Stud. Org. Chem.* **1987**, *31*, 461–468.
(3) Bordwell, F. G.; Satish, A. V.; Jordan, F.; Rios, C. B.; Chung, A. C. *J. Am. Chem. Soc.* **1990**, *112*, 792–797.
(4) Barletta, G.; Chung, A. C.; Rios, C. B.; Jordan, F.; Schlegel, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 8144–8149.

0022-3263/91/1956-5029$02.50/0

by Hopmann and Brugnoni[5] to between 17 and 19,[6] based on the kinetics of isotope exchange at the C2 position in acidic medium, and experiments that appear to support the supposition of diffusion-controlled reprotonation of the ylide. Those authors also presented structure–activity correlations that were consistent with carbanion, rather than with carbene-like reactivity. In a very recent contribution Bordwell and Satish presented further evidence consistent with a pK_a higher than 16 in Me_2SO for thiazolium ions at C2H, and based on experiments in which a variety of reagents failed to trap the ylide, offered support for carbanionic, rather than carbene-like behavior.[7] The structure and reactivity of the ylide remains an enigma, in spite of many reports in the literature concerning its chemistry.[7,8] In a recent series of articles isolation and NMR characterization of "thiamin ylide" was claimed.[9]

This study was undertaken in an attempt to spectroscopically observe and to reexamine the chemical behavior of the thiazolium ylide under nonaqueous, aprotic conditions. Under these conditions, the conjugate bases at C2 of thiazolium[10,11] and imidazolium[12] ions had been reported to give rise to condensation products, in many cases self-condensation,[13,14] such that the C2 atoms of two molecules are linked by a C=C bond. The formation of such syn/anti symmetrical dimers can be rationalized by either carbene (insertion) or carbanion-type (addition) behavior. This report summarizes several novel experi-



(2)

ments designed to differentiate among the mechanisms leading to dimer formation. Based on our success in generating the enamine 2,[2] we decided to attempt quantitative generation of the ylide under the same conditions. To elucidate the reactivity of the ylide **1b**, two [2-^{13}C]-thiazolium compounds were synthesized: 3,4,5-trimethyl[2-^{13}C]thiazolium nitrate (**3**) and 3-benzyl-5-(β-ethoxyethyl)-4-methyl[2-^{13}C]thiazolium bromide (**4**). A variety of structures along the dimerization path could be identified, and the end products were consistent with previous reports that relied solely on product analysis.[10,11] Identification of a hitherto undetected unsymmetrical dimer, in which C2 atoms of two thiazolium ions are bonded to each other, as a precursor to the syn/anti symmetrical dimers, enabled us to perform novel experiments to explore the reactivity of the thiazolium conjugate base

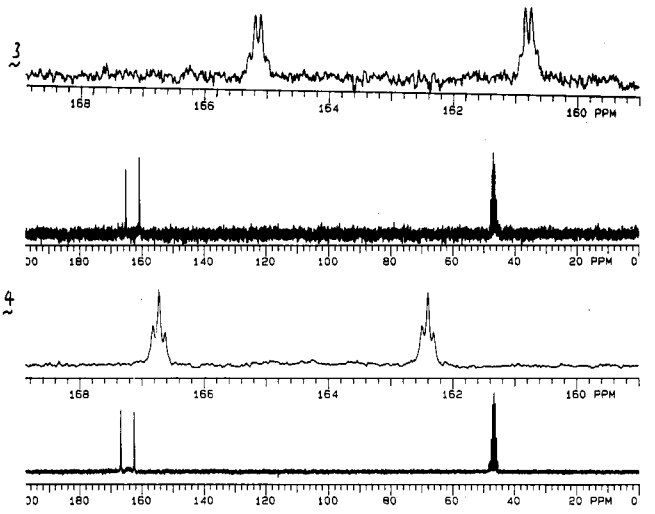


Figure 1. Proton coupled ^{13}C spectra at the enriched C2 positions of compounds **3** (99 atom % enriched) and **4** (91.9 atom % enriched) recorded at 50.31 MHz in Me_2SO. To obtain the chemical shift referenced against TMS and shown in Table I, ca. 7.5 ppm must be subtracted from those numbers shown in this figure.

under aprotic conditions. In one approach "crossover" on formation of the unsymmetrical dimer from [2-^{13}C]-H and [2-^{13}C]-D species was monitored. In the other, 3-alkenylthiazolium ions were synthesized, that, had insertion reactivity resulted, should have led to cyclopropane formation. The sum of the results is consistent with the C2 atom of the conjugate base undergoing addition, rather than insertion reactions. While compound **4** was found to be more reactive than **3**, evidence is presented that indicates a similar pathway for dimerization from both salts.

On account of the fundamental importance of the chemical behavior of the thiazolium ylide in thiamin biochemistry, the results here reported take on special significance.

Results and Discussion

Due to the relatively slow time frame of the ^{13}C NMR observation even on highly enriched compounds, the results reported refer to essentially steady-state conditions for a particular concentration ratio of thiazolium to base. Based on such experiments, it is difficult to quantify rate constants leading to intermediates or products. On the other hand, one can ascertain which structure predominates under a certain set of conditions and the sequence of reactions.

Synthesis and ^{13}C NMR Data of Thiazolium Salts 3 and 4. Both labelled thiazolium ions were synthesized starting from ^{13}C-labeled thiourea. The synthesis of **3** started with the condensation of [^{13}C]thiourea with 3-chlorobutanone, followed by diazotization and finally quaternization at the ring nitrogen using methyl iodide. The synthesis of **4** started with condensation of ^{13}C-labeled thiourea with 3-chloro-4-oxopentylethanoate, followed by diazotization to remove the 2-amino group from the thiazole ring, alkylation of the β-hydroxyethyl group with ethyl bromide, and finally quaternization of the ring nitrogen using benzyl bromide.

Figure 1 presents the coupled spectra of the starting materials. The one bond and three bond (to the NCH_3 and NCH_2, respectively) coupling patterns and the magnitude of the coupling constants (Table I) confirms the assignment of the label to the C2 position.[8]

A. Reactivity of *N*-Methylthiazolium 3 in the Presence of *tert*-Butoxide. 1. Product Distribution,

(5) Hopmann, R. F. W.; Brugnoni, G. P. *Nature (London) New Biol.* **1973**, *246*, 157–158.
(6) (a) Washabaugh, M. W.; Jencks, W. P. *Biochemistry* **1988**, *27*, 5044–5053. (b) Washabaugh, M. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 674–683. (c) Washabaugh, M. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 683–692.
(7) Bordwell, F. G.; Satish, A. V. *J. Am. Chem. Soc.* **1991**, *113*, 985–990.
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(9) (a) Sugimoto, H.; Hirai, K. *Tetrahedron Lett.* **1985**, *26*, 883–886. (b) Sugimoto, H.; Hirai, K. *Heterocycles* **1987**, *26*, 13–17. (c) Sugimoto, H.; Hirai, K. *Heterocycles* **1988**, *27*, 877–880. (d) Sugimoto, H.; Ishiba, T.; Sato, T.; Nakai, H.; Hirai, K. *J. Org. Chem.* **1990**, *55*, 467–470.
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(15) Echols, R. E.; Levy, G. C. *J. Org. Chem.* **1974**, *39*, 1321–1322.

Table I. ^{13}C NMR Chemical Shifts of the C2 Atoms in Starting Materials and Products Produced by *tert*-Butoxide in Me_2SO[a]

	compound 3 δ	compound 4 δ
starting material	155.214	156.794
unsymmetrical dimer	66.24 (d, 1 C, J = 58 Hz)	
	173.37 (d, 1 C, J = 58 Hz)	
syn/anti dimers	116.43, 113.56	128.72, 127.43
rearranged dimer		81.63 (d, 1 C, J = 61 Hz)
		169.04 (d, 1 C, J = 61 Hz)

[a] Measured in ppm downfield from TMS.

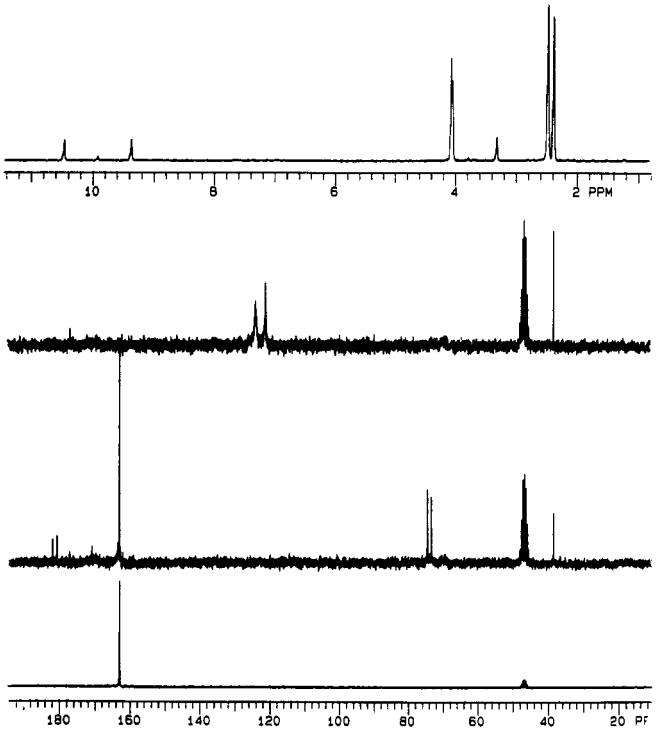
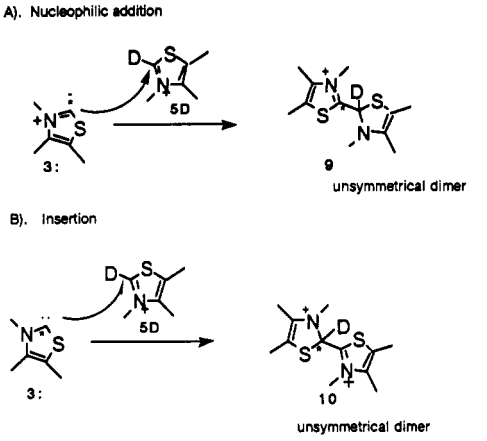


Figure 2. Proton decoupled ^{13}C spectrum of compound 3 in Me_2SO (bottom spectrum); on addition of ca. 1 equiv of *t*-BuOK (second from the bottom); on addition of excess base (second from the top); the proton NMR spectrum in the absence of base (top). To obtain the chemical shifts referenced against TMS and shown in Tables I and II, ca. 7.5 ppm must be subtracted from those numbers shown in this figure.

Identification of an Unsymmetrical Dimer. The progression on adding one equivalent or great excess of *tert*-butoxide to 3 is shown in Figure 2. At the top the ^1H, at the bottom the broad-band decoupled ^{13}C spectra are presented in the absence of base. Selected population transfer[16] techniques (enabling differentiation of protonated and nonprotonated carbons) clearly indicated that on addition of 1 equiv of base a dimer was being formed in which a highly deshielded quaternary C2 was bonded to a shielded protonated C2 (second spectrum from the bottom in Figure 2). This species will be referred to as the unsymmetrical dimer. On addition of excess base two new resonances appeared near 115 ppm (second spectrum from the top in Figure 2). Neither resonance gave evidence of either directly attached protons or of being coupled to another C2 atom. These resonances therefore can be assigned to the highly symmetrical syn and anti dimers 27,

(16) Benn, R.; Gunther, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 350–380.

Scheme I. Two Mechanisms Proposed To Account for the Formation of Unsymmetrical Dimers

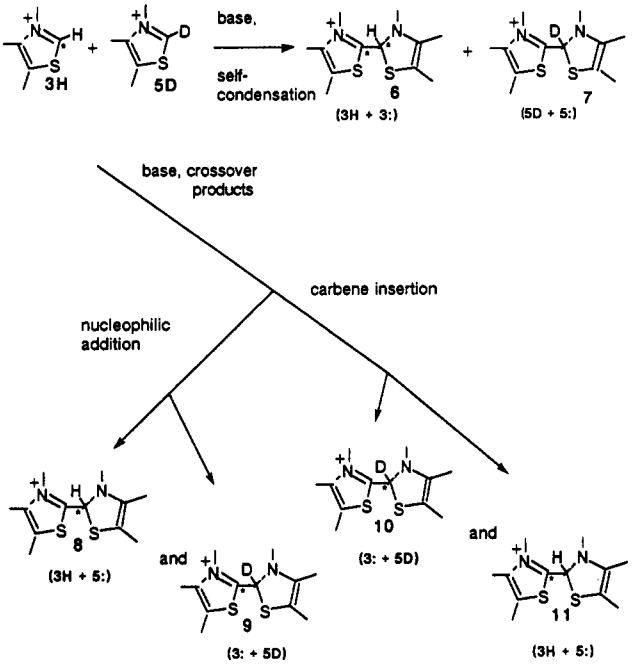


in which the C2 atoms are in identical environments, hence are not coupled to each other. Such a dimer (as a syn/anti mixture) had been synthesized by Doughty from the 5-carbethoxy-3-methylthiazolium,[10] and from 3-methylbenzothiazolium by Baldwin and co-workers.[14] The sequence of reactions indicated in eq 2 was found to be reversible, since on addition of acid the starting material was regenerated (according to both UV and proton NMR, data not shown). The acid regeneration of starting materials from the syn/anti mixture was also shown by Doughty.[10] The well-known side reaction of thiazolium compounds, base-catalyzed ring opening, would be totally inconsistent with the observations.

Very importantly, no resonance of any significant size was found between 0 and 600 ppm that could be assigned to the ylide/carbene. Rather, for a concentration ratio of base to 3 of about unity the thiazolium and the unsymmetrical dimer very clearly coexist. The sequence of events on addition of base indicates that the unsymmetrical dimer is formed first, followed by the syn/anti dimer. The initial formation of unsymmetrical dimer in the presence of base *rules out direct dimerization of two carbenes* as a mechanistic choice. The lifetime of the ylide must be very short, as least on the time scale of the rather slow NMR observation. If there is a steady-state concentration of the ylide built up, we have not detected it. The forward rate constants for ylide formation have been extensively studied by several groups, most recently by Washabaugh and Jencks.[6] Under our conditions, the rate of formation of unsymmetrical dimer from ylide and thiazolium ion appears to be greater than reprotonation of the ylide to starting material. While this may appear surprising at a first glance, the relative p*K*s of *t*-BuOH and thiazolium ion in the solvent employed make it plausible (see below).

2. Is the Unsymetrical Dimer Formed by Addition or Insertion? According to Wanzlik,[12] Metzger,[13] and Risinger and Doughty,[10,11] the formation of the syn/anti symmetrical dimers, such as 27 in eq 2, is consistent with "direct" dimerization of two molecules of conjugate base, i.e. ylide. Metzger and co-workers recognized that there were three possibilities to explain symmetrical dimer formation: direct dimerization of two carbenes, insertion followed by deprotonation, and nucleophilic addition followed by deprotonation.[13] For compound 3 we have ruled out direct dimerization of two ylides by observing the unsymmetrical dimer intermediate that is a precursor to the symmetric dimer. In order to decide whether formation of the unsymmetrical dimer proceeds via addition or insertion, we employed two different approaches, whose utility is absolutely dependent on our ability to directly

Scheme II. Possible Unsymmetrical Dimers Formed during Crossover

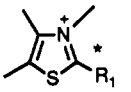


observe the unsymetrical dimer, that from **3** is rather stable in the absence of large excess of base.

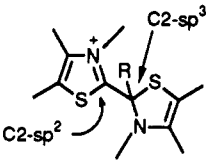
a. Crossover Experiments: The Working Hypothesis According to Scheme I. Appropriately labeled materials corresponding to species **3H** (compound **3**) and **5D** [3,4,5-trimethylthiazolium-2-*d*] were used. Their conjugate bases are denoted as **3:** and **5:** respectively, whereas the star denotes the ^{13}C isotope, the unstarred carbon the ^{12}C. If the formation of unsymmetrical dimer can be monitored prior to equilibration of hydrogen isotopes among the starting materials, the immediate product formed should be informative as to whether addition or insertion had taken place.

In order for the experiment to provide interpretable results, several conditions must be fulfilled simultaneously: (1) the proton and deuteron label in **3H** and **5D** may not be fully interchanged during the formation of the unsymmetrical dimer, i.e. the reprotonation to thiazolium ion by the conjugate acid of the base employed must be slower than formation of the unsymmetrical adduct, and equilibration of H and D among the various species must be slower than the time required for the NMR measurement; (2) all unsymmetrical adducts resulting from the crossover experiments must be distinguishable from each other and from the products of self-condensation. Scheme II shows the products of crossover expected in the absence of H/D scrambling in the starting materials prior to formation of the unsymmetrical adducts. Under each dimer the species leading to them are indicated in parentheses. That there is no immediate equilibration of the proton and deuteron between **3H** and **5D** will be evident from some time-dependent experiments presented below. The concentration of base used was always insufficient to convert most starting material to products, so that starting material and unsymmetrical dimer could be observed simultaneously, and in the absence of significant conversion to the symmetrical dimer. Assuming that the upper limit for the thiazolium pK_a in Me_2SO is that observed in water (18–19),[6,7] and the known pK_a of *tert*-butyl alcohol (32)[17] in this solvent, transfer of proton or deuteron from *t*-BuOH to the ylide is thermodynamically highly unfavorable, hence dimerization can compete effectively. This would hold even if proton transfer from *t*-BuOH to the ylide proceeded at a diffusion controlled second-order rate constant (say 10^{10} M^{-1} s^{-1}). Under dry conditions, the first condition may be fulfilled.

Table II. ^{13}C NMR Chemical Shifts[a] at C2[b] in 3-Methylthiazolium Ions and Unsymmetrical Dimers Produced by *t*-BuOK in DMSO-d_6 (75 MHz)



R_1	δ at C2
H (**3H**)	155.89
D (**5D**)	155.56 (t, 1 C, J = 33.9 Hz)



	R	C2-sp²	C2-sp³	δ at C2-sp²	δ at C2-sp³
11	H	*		173.97	
8	H		*		66.38
9	D	*		173.89	
10	D		*		66.15 (t, 1 C, J = 28.0 Hz)
6	H	*	*	173.96 (d, 1 C, J = 58.1 Hz)	66.36 (d, 1 C, J = 58.1 Hz)
12	D	*	*	173.88 (d, 1 C, J = 57.8 Hz)	

[a] In parts per million relative to TMS. [b] An asterisk (*) denotes a ^{13}C enriched position.

In order to demonstrate whether the second condition is satisfied, i.e. whether all isotopically distinct species can be differentiated in the same NMR tube by ^{13}C NMR, the reaction outlined is Scheme II was performed with a ca. equimolar mixture of **3H** and **3D** resulting in the formation of all unsymmetrical dimer species. Under these conditions, and with proton decoupling, the resonances corresponding to all distinct ^{13}C environments (**6**, **8**, **9**, **10**, **11**, and **12**) could be assigned by virtue of the facts that: (a) only the self-condensed unsymmetrical dimers (**6** and **12**) give rise to doublets in both the tetrahedral and trigonal chemical shift region; (b) direct one-bond coupling to deuteron gives a characteristic 1:1:1 triplet for the ^{13}C resonance (**10**), while those ^{13}C nuclei attached to protons give rise to singlets under broad-band decoupling conditions (**8**), and are also subject to nuclear Overhauser enhancements (NOEs); (c) deuteron either directly attached to ^{13}C (**10**) or two bonds away from ^{13}C (**9**) will cause an upfield chemical shift compared to a proton in the same position (albeit the two-bond chemical shift is only ca 0.08 ppm, yet readily observed).[18]

The isotope effect on the chemical shift and the different coupling patterns enabled us to identify the isotopic connectivities of *each* unsymmetrical dimer in the same NMR tube (see Table II for the chemical shift and multiplicity of each isotopically distinct unsymmetrical dimer). There are some caveats to this scheme. Extra effort must be made to maintain the solution as moisture free as possible.

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(18) Kunzer, H.; Cottrell, C. E.; Paquette, L. A. *J. Am. Chem. Soc.* **1986**, *108*, 8089–8091.

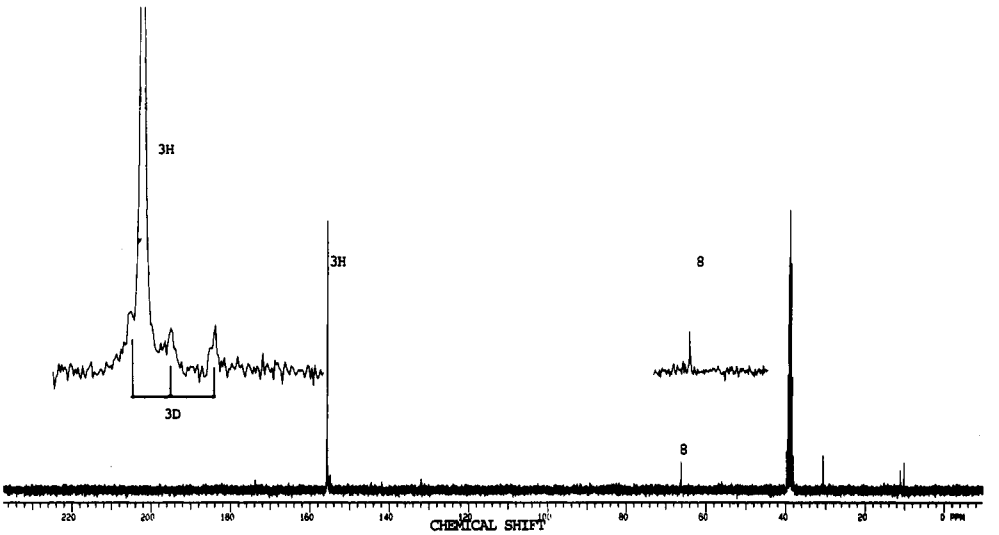


Figure 3. Broad-band proton decoupled ^{13}C spectrum of a mixture of **3H** (0.0189 mmol) and **5D** (0.122 mmol) on the addition of *t*-BuOK (0.122 mmol) in Me_2SO recorded at 75 MHz. Scheme II provides relevant structures; enlarged spectrum of the key resonances is shown.

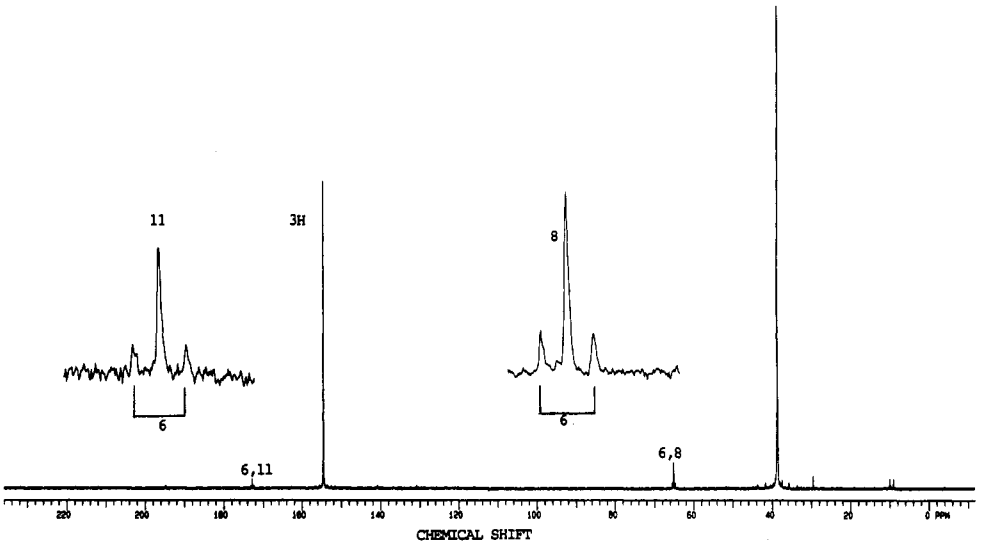


Figure 4. Broad-band proton decoupled ^{13}C spectrum of a mixture of **3H** (0.0494 mmol) and **5D** (0.051 mmol) on the addition of *t*-BuOK (0.08 mmol) in Me_2SO recorded at 75 MHz. Scheme II provides relevant structures; enlarged spectrum of the key resonances is shown.

The deuteron directly bonded to the ^{13}C resonance significantly lengthens the spin–lattice relaxation time of the attached ^{13}C, making integration, and relative concentration estimates of such species (i.e. **10**), rather unreliable, unless unreasonably long recycle times are used.

b. Crossover Experiments Are Consistent with Addition, Rather Than Insertion. Figure 3 presents the ^{13}C NMR spectrum of a solution resulting from mixing of **3H** (0.0189 mmol) and **5D** (0.122 mmol) with 0.122 mmol of *t*-BuOK under broad-band decoupling conditions. Under these conditions of low percent conversion (compare the height of starting material **3H** to that of unsymmetrical dimer **8**), adducts resulting from self-condensation are minimized, as reflected by the absence of doublets in both the sp^2 and sp^3 regions of the spectrum. The starting materials at 156 ppm (singlet for **3H**, and 1:1:1 triplet for **3D**), and unsymmetrical dimer at 66.37 ppm in the sp^3 region corresponding to **8** are visible, the latter being consistent with addition of **5**: to **3H**.

Figure 4 presents the ^{13}C NMR spectrum that results when nearly equimolar concentration of **3H** (0.0494 mmol) and **5D** (0.051 mmol) are mixed with 0.08 mmol of *t*-BuOK under broad-band decoupling conditions. In this spectrum the self-condensation product **6** is evident from the appearance of the characteristic doublets both in the high-field and the low-field regions. In between the two limbs of the doublets are visible singlets characteristic of **8** and **11**. Also noteworthy are several other features clearly gleaned from this spectrum: (a) the amount of base added is not nearly sufficient to convert most of the starting material to the unsymmetrical adducts; (b) the reaction does not proceed to any significant extent to the symmetrical syn/anti dimers; (c) starting material **3H** has not undergone H/D exchange; (d) the intensities of resonances in the tetrahedral carbon chemical shift range are consistently and significantly higher than those downfield in the trigonal carbon range, confirming the protonated nature of the former (i.e. we are observing NOEs, as expected under broad-band decoupling conditions); (e) while the formation of **8** is consistent with addition, formation of **6** and **11** is only consistent if there are two different kinetic isotope effects operating, i.e. deprotonation of **3H** is faster than dedeuteration of **5D** (is expected based on the report by Washabaugh and Jencks),[6c] and addition of **3**: or **5**: to **3H** is faster than to **5D** (we have found no relevant isotope effect for this contention).

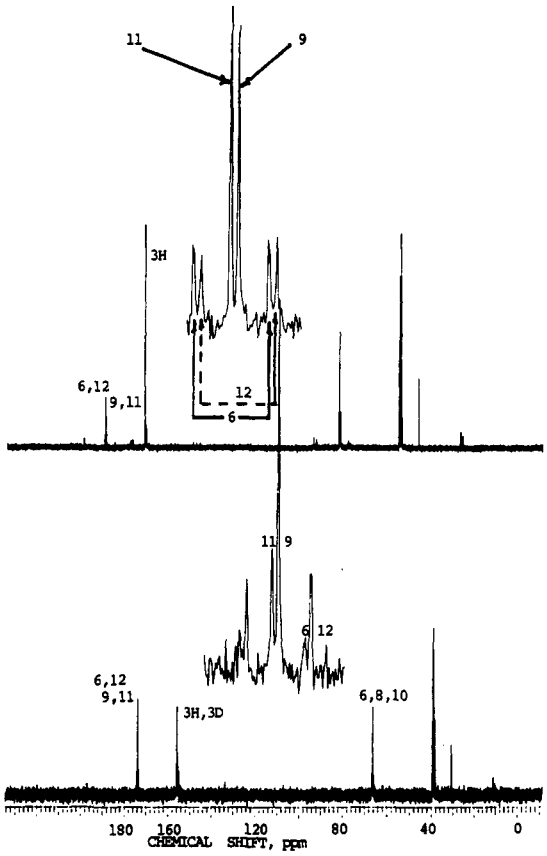


Figure 5. Broad-band proton decoupled ^{13}C spectrum of a mixture of **3H** (0.091 mmol) and **5D** (0.154 mmol) on the addition of *t*-BuOK (0.21 mmol) in Me_2SO recorded within 3 h of mixing at 75 MHz (lower spectrum) and recorded 4 days later (upper spectrum). Scheme II provides relevant structures; enlarged spectrum of the key resonances is shown.

Figure 5 presents the ^{13}C NMR spectrum, demonstrating the time development of the reaction products on mixing **3H** (0.091 mmol) and **5D** (0.154 mmol) with 0.21 mmol *t*-BuOK. The group of resonances in the trigonal carbon chemical shift region of the unsymmetrical dimers are detailed at 3 h (the time required to be able to observe all resonances shown with an acceptable signal/noise ratio) in the lower spectrum, and 4 days (upper spectrum) after mixing of reagents: a doublet corresponding to **6**, a doublet for **12**, a singlet for **11**, and a singlet for **9**. During this experiment several products were formed, indicating that there had taken place some H/D equilibration between **3H** and **5D** prior to, or concomitant with, formation of the unsymmetrical adducts. What makes the experiment useful, is that the spectrum recorded 4 days after mixing looks very different from that ca. 3 h after mixing. Most telling from the point of view of the crossover experiment is the behavior of the resonances corresponding to species **9** vs **11**, since self-condensation products are not informative. At 3 h after initiation of the reaction [**9**] ≫ [**11**]. After 4 days, those species are at nearly equal concentrations according to the intensities of the resonances. The resonances that predominate at early times correspond to those unsymmetrical dimers expected based on addition according to Scheme II. During 4 days of equilibration there is further H/D exchange taking place. This slow, further H/D exchange apparent in the spectra may have two sources. The C2-H and C2-D in the unsymmetrical dimers may have undergone further proton (deuteron) loss to yield the symmetrical dimer and then reverted to unsymmetrical dimer being redeuterated or reprotonated. Alternatively, the unsymmetrical dimer may undergo slow reversion to thiazolium starting material, whose H/D has now been further equilibrated, thus yielding essentially statistically distributed unsymmetrical dimers. Indeed, the 4-day spectrum does give evidence of the presence of some small concentration of the syn/anti symmetrical dimer set. Also, the reactions depicted in eq 2 are readily reversible in aqueous acid, hence will proceed at a finite, albeit obviously very slow, rate even in the solution here used. Irrespective of the source of the slow H/D equilibration observed, what is crucial is that based on the comparison of the relative concentrations of [**9**] and [**11**] in the trigonal carbon chemical shift region, one can extrapolate back to short reaction times (not readily quantifiable even with highly enriched samples) and conclude that species **9** rather than **11** was formed first, hence the *initial formation of the unsymmetrical dimers must have taken place by addition, not insertion.*

Figure 5 provides further support for the validity of the crossover experiments. When we monitored the formation of unsymmetrical dimer by proton NMR, within the few minutes required to record the spectrum after mixing the reactants, the unsymmetrical dimer was already formed and the resonance corresponding to it underwent no further time-dependent changes, i.e. conversion to symmetrical dimer. As seen in Figure 5, the H/D exchange in starting materials and products may have half-lives of hours, perhaps days, depending on the dryness of the solution.

It was found that in addition to *t*-BuOK, *s*-BuLi and $(Me_3Si)_2NNa$ could also perform the reaction in the same solvent. As an example, in Figure 6 a ^{13}C NMR spectrum

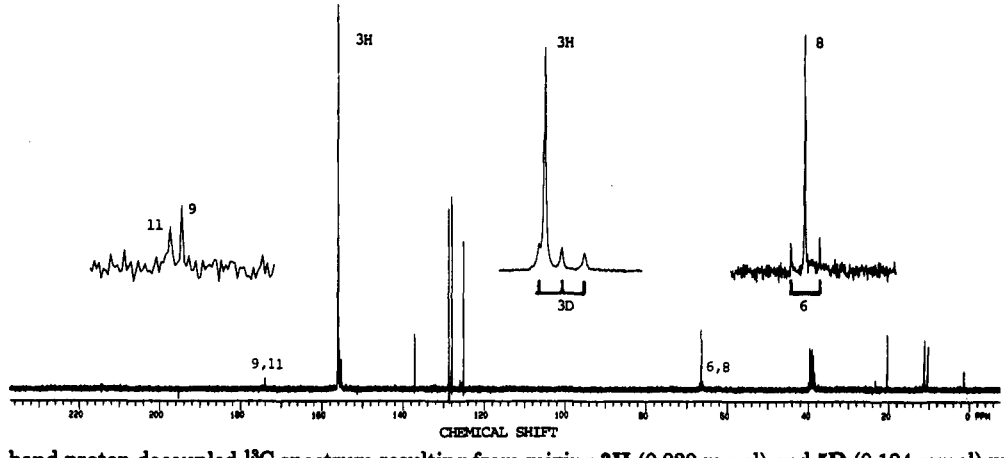
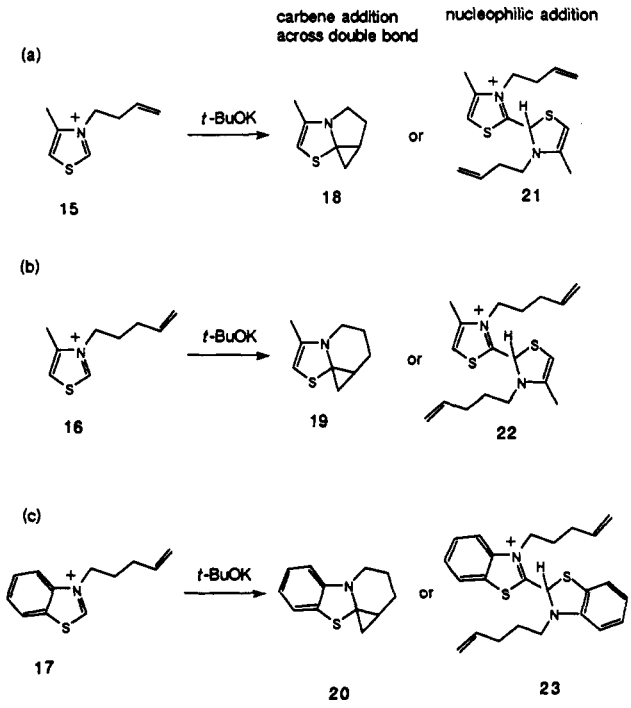


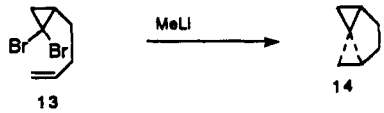
Figure 6. Broad-band proton decoupled ^{13}C spectrum resulting from mixing **3H** (0.030 mmol) and **5D** (0.124 mmol) with $(Me_3Si)_2NNa$ (0.115 mmol) in Me_2SO at 75 MHz. Scheme II provides relevant structures; enlarged spectrum of the key resonances is shown.

Scheme III. Structure of Products Expected during the Reaction of *N*-Alkenylthiazolium Ions with Base



resulting from mixing **3H** (0.030 mmol) and **5D** (0.124 mmol) with $(Me_3Si)_2NNa$ (0.115 mmol) in Me_2SO is presented. The observation of predominant **8** and **9**, with no evidence of **10** (not surprising in view of the relaxation problem induced by the attached deuteron), and of a smaller amount of **11** compared to **9**, again is consistent with an addition mechanism.

c. Reactions of *N*-Alkenylthiazolium Salts in the Presence of *t*-BuOK: Intramolecular vs Intermolecular Addition. Based on results from Wiberg's laboratory,[19] where compound **13** was shown to yield **14**, presumably by addition of the carbene across the unactivated double bond, three thiazolium salts quarternized with alkenyl side chains were synthesized (**15**–**17** in Scheme III).

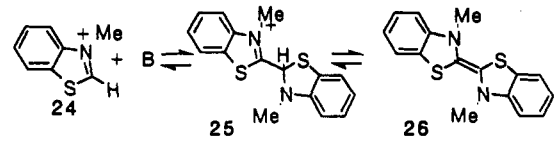


(3)

The thiazolium salts were treated with *t*-BuOK in DMSO-d_6, and the products of the reactions were monitored by ^1H NMR. Carbene reactivity should manifest itself by intramolecular addition to the double bond to form a tricyclic compound. ^1H NMR would be able to monitor the disappearance of the resonances corresponding to the vinyl protons. Nucleophilic addition would be evident from formation of the unsymmetrical dimers, as above. The latter sometimes can be detected by proton NMR, since the C2-H of the unsymmetrical dimer has a very characteristic proton chemical shift between 6.5 and 7.4 ppm, depending on the thiazolium starting material.

When 3-(3-butenyl)-4-methylthiazolium bromide (**15**) was treated with *t*-BuOK, a doublet at δ 6.642 and 6.637 was observed under conditions that led to consumption of 60% of the thiazolium ion. On the other hand, the intensities of resonances at δ 5.9–4.5 corresponding to protons along the double bond remained the same. The chemical shift of the doublet corresponding to C2-H in **21** is the same as that observed under the same conditions for the proton NMR of unsymmetrical dimer formed from 3,4,5-trimethylthiazolium ion. These results are consistent with formation of the unsymmetrical dimer **21**, but not with the tricyclic structure **18**. Compound **16** was designed to allow formation of a six-membered ring on carbene addition (were it to be formed), rather than the five-membered ring that would have been formed from **15**. When 4-methyl-3-(4-pentenyl)-thiazolium bromide (**16**) was treated with *t*-BuOK in DMSO-d_6, a doublet at δ 6.652 and 6.648 resulted in the ^1H NMR spectrum. When comparing with the spectrum of the starting material, the resonance at δ 10.2 corresponding to C2-H decreased in intensity, but the intensities of the resonances in the δ 5–6 range corresponding to the vinyl protons remained the same. Again, the unsymmetrical dimer **22** was formed in preference to the tricyclic compound **19**.

Based on detection of the symmetrical dimer **26** from *N*-methylbenzothiazolium ion **24**, in base, Metzger and co-workers deduced direct dimerization of carbenes as a likely mechanism for thiazolium dimerization.[13] In an attempt to determine whether benzothiazolium ion behaves differently from the previous alkylthiazolium ions, the previous test was applied. In a control experiment *N*-methylbenzothiazolium iodide **24** was treated with *t*-BuOK in DMSO-d_6, and a singlet resonance at δ 7.24 corresponding to C2-H in the unsymmetrical dimer **25** was observed in the ^1H NMR spectrum. This resonance is further downfield than the resonance corresponding to C2-H of the unsymmetrical dimer derived from alkylthiazolium ions. This resonance is also more difficult to monitor than that for **21** and **22**, probably because of the greater tendency of this unsymmetrical dimer to undergo further deprotonation to form a stable symmetrical dimer **26**. The faster data acquisition in proton NMR, however, enables ready detection of the initial formation of the unsymmetrical dimer even from benzothiazolium ion, ruling out a direct carbene dimerization mechanism for eq 4.



(4)

Next, 3-(4-pentenyl)benzothiazolium bromide **17** was subjected to *t*-BuOK in DMSO-d_6. Several resonances in the δ 6.4–7.1 region were observed. They may correspond to hydrogens in the unsymmetrical dimer **23** due to the highly rigid delocalized structures. After further addition of base, the resonance at δ 10.4 corresponding to C2-H in the starting material diminished further in intensity, and the resonances pertaining to the phenyl ring (δ 7.8–8.6) shifted to higher field. This experiment confirms that a symmetrical dimer is formed in accord with Metzger's report.[13] But the intensities of the resonances in the δ 5–5.2 region, corresponding to hydrogens along the double bond remained the same. While in this complicated spectrum the resonance characteristic of the C2-H in the unsymmetrical dimer is difficult to detect, the fact that the vinyl region remained unchanged during the reaction demonstrates that intermolecular reaction, presumably nucleophilic addition, again took precedent over intramolecular carbenic addition that would have resulted in cyclopropane formation. Formation of a syn/anti dimer from 3-alkylbenzothiazolium salt had also been reported by Baldwin and Walker.[14a]

(19) Wiberg, K. B.; Chaves, A. *J. Am. Chem. Soc.* **1989**, *111*, 8052–8053.

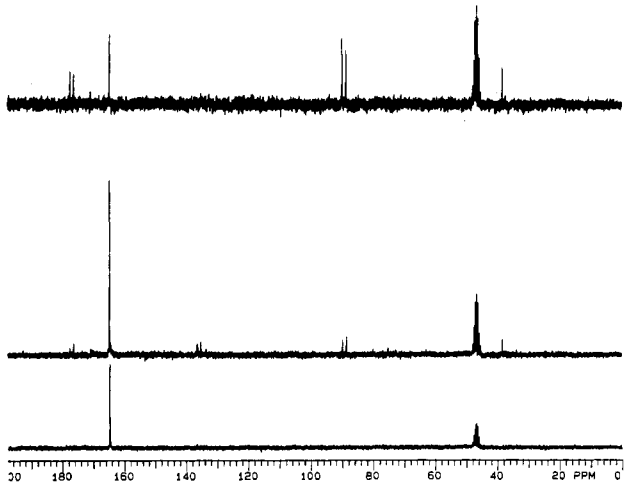


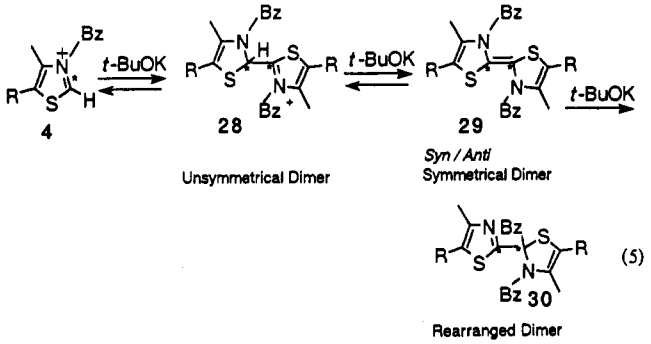
Figure 7. Proton decoupled ^{13}C spectrum of compound **4** in Me_2SO (bottom spectrum); on addition of approximately one equivalent of *t*-BuOK (middle); and on further addition of excess base (top spectrum). To obtain the chemical shifts referenced against TMS, and shown in Table I, ca. 7.5 ppm must be subtracted from those numbers shown in this figure.

As an added control, a further intermolecular reaction was also attempted to prove this point. A sample of 3,4,5-trimethyl[2-^{13}C]thiazolium nitrate **3** was mixed with excess cyclohexene in DMSO-d_6 and then subjected to *t*-BuOK. The reaction mixture was monitored by proton decoupled ^{13}C NMR. The spectrum showed no resonances corresponding to new structures, only those corresponding to the unsymmetrical dimer.

In the experiments using **15–17**, by virtue of the entropic advantage conditions are loaded in favor of cyclopropane formation (were it a possibility). Yet, in all three cases studied (i.e. irrespective of the size of the tricyclic ring that would result, five- or six-membered ring, or whether the more reactive 3-methylbenzothiazolium ion is employed), evidence could only be obtained for the intermolecular reaction.

d. Molecular Mechanics Calculations. Molecular Mechanics[20] calculations were performed on the syn and anti symmetrical dimers **29**, assuming a planar geometry. It was found that the two geometric isomers had nearly equal energies, in accord with the fact that every time we repeated the experiment the ratio of integrals for the resonances near 115 ppm remained nearly the same. The calculated energies for the two isomers converged to within 0.1 kcal of each other.

2. Reactivity of *N*-Benzylthiazolium 4 in the Presence of *tert*-Butoxide. Figure 7 shows that on addition of *tert*-butoxide, on the slow time scale of the ^{13}C NMR, compound **4** is converted to a compound that gives rise to two resonances at δ 127.4 and 128.7, neither exhibiting either coupling to an other C2 atom, or directly bonded proton. These resonances pertain to the syn/anti symmetrical dimers. With time, or with excess base, two doublets appear with identical coupling constants near 82 and 169 ppm ($^1J_{C-C}$ = 61 Hz). The carbon atoms that give rise to these resonances have no directly attached protons. They correspond to a rearranged dimer, as shown by Doughty for the 3-benzyl-5-carbethoxythiazolium ions and for thiamin[10] and Baldwin et al. for the *N*-benzylbenzothiazolium ion.[14] The carbon chemical shift of the C2 of the aromatic thiazole in the rearranged dimer formed from 3-benzylbenzothiazolium salt was noted to be highly deshielded (ca. 172.5 ppm in $CHCl_3$),[14a] similar to the 169 ppm value quoted by us. Again, no evidence was found in any of the experiments for any trace of ylide. We thus confirmed earlier work on the thiazolium salts bearing bulky, electron-withdrawing substituents at N-3. Ours is the first report of the formation of the syn/anti dimer (rather than only of the rearranged dimer) from a 3-benzylthiazolium salt, since the syn/anti dimer had earlier been observed only from the benzothiazolium precursor.[14] CMR failed to give evidence for the intermediacy of **28**, presumably due to the slow data acquisition and short life time of the species.



(5)

Rearranged Dimer

In an attempt to establish the intermediacy of **28**, we monitored the reaction of 3-benzyl-4,5-dimethylthiazolium bromide **39** (0.1 M) on addition of *t*-BuOK (0.1 M) in Me_2SO by proton NMR. It was anticipated on the basis of previous results that, in the unsymmetrical dimer, resonances corresponding to the CH_2 of the benzyl group (located in a chemical shift region that has no resonances other than those pertaining to the benzylic methylenes), and the single remaining C2-H (see section **1c** for related chemical shifts), may be detectible. The CH_2 for **39** (δ 5.80), and for rearranged dimer are readily assigned (the latter as two AB quartets: δ 4.43, J_{AB} = 17 Hz, $\Delta\nu$ = 0.25 ppm, and δ 3.55, J_{AB} = 13 Hz, $\Delta\nu$ = 0.16 ppm, in accord with Baldwin and Walker[14b]). In addition, there was a singlet assignable to the benzylic methylene in the syn/anti symmetrical dimer at δ 4.21 that disappeared on total conversion of **39** to the rearranged dimer. Most importantly, in this rather complex spectrum, there were two resonances clearly apparent within the first minute required to mix the base, insert the tube into the probe, and acquire the data: near δ 7.12 and δ 4.33 ppm (consistent with that expected for the C2-H, and benzylic methylene resonance, respectively, the latter attached to a neutral thiazoline ring, i.e. similar in chemical shift to those observed for benzylic protons of the rearranged dimer). Both of these resonances disappeared within ca. 5–10 min of mixing, while resonances assignable to the symmetrical and rearranged dimer persisted for an hour and longer. If there was only a fraction of an equivalent of base to thiazolium added, these two resonances again reappeared on injection of additional base, then quickly disappeared. A difference spectrum between 1 and 3 min of mixing showed decrease of the δ 7.12 and 4.33 resonances, slower decrease of the one corresponding to symmetrical dimer at δ 4.21, and growth of the two AB quartets corresponding to rearranged dimers. We believe that the δ 7.12 and 4.33 resonances

(20) (a) Haake, P.; Duclos, J. M. *Tetrahedron Lett.* **1970**, *6*, 461–464. (b) Ilvespaa, A. O. *Helv. Chim. Acta* **1968**, *51*, 1723–1733. (c) McKillop, A.; Sayer, T. S. B.; Bellinger, G. C. *J. Org. Chem.* **1976**, *41*, 1328–1331.

(21) Williams, D. L.; Ronzio, A. R. *J. Am. Chem. Soc.* **1952**, *74*, 2409–2410.

(22) (a) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535–3536. (b) Iwashige, T.; Saeki, H. *Chem. Pharm. Bull. Jpn.* **1967**, *15*, 1803–1808.

(23) Monera, O. D.; Chang, M.; Means, G. E. *J. Org. Chem.* **1989**, *54*, 5424–5426.

(24) (a) Allinger, N. L.; Tribble, M. T., Miller, M. A., Wertz, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 1637–1648. (b) Allinger, N. L. *Adv. Phys. Org. Chem.* **1976**, *13*, 1–82.

pertain to the unsymmetrical dimer that is fully formed before we can acquire the spectrum. We conclude that the dimerization of the 3-benzyl analogues studied by several groups, as well as of thiamin,[10] also proceeds via this unsymmetrical dimer, as shown in eq 5. Due to the short life time of the unsymmetrical dimer in this case, efforts to observe it by ^{13}C NMR have proven futile. We have no reason to doubt, that the formation of the unsymmetrical dimer from 3-benzyl- and 3-methylthiazolium salts follows the same mechanism, addition.

Conclusions

An important accomplishment of this study is the demonstration for the first time of the existence of the unsymmetrical dimer intermediate on the pathway to the syn/anti dimer from both *N*-methyl (**3**), and *N*-benzyl (**4**) salts. The symmetrical dimer derived from **3** is quite stable and has no tendency to rearrange. Because of the enhanced stabilities of both unsymmetrical and symmetrical dimers formed from **3**, this compound lent itself to further, more subtle mechanistic investigation. For compound **4** the unsymmetrical dimer was too short-lived to be detectible on the slow ^{13}C NMR time scale, yet it could be detected within a few minutes of mixing by proton magnetic resonance. The syn/anti symmetrical dimer from **4** readily proceeds to the rearranged dimer. One can speculate why **3** and **4** should behave so differently. One possibility is that the C2-H of the unsymmetrical dimer formed from **4** is much more acidic than the corresponding position derived from **3**, due to the electron-withdrawing effect of the benzyl groups. The benzyl group undergoes a [1,3]-sigmatropic rearrangement, presumably to relieve the steric strain in the planar symmetrical dimer. It was demonstrated by Baldwin and co-workers that such rearrangements from 3-allyl- and 3-benzylthiazolium salts take place by a free radical mechanism.[14]

Had the unsymmetrical dimer not been observed as a precursor to the symmetrical dimer for **3**, the sequence of steps would have been unclear. Were the symmetrical dimer the first compound formed from the ylide, the intervention of carbenic chemistry may be invoked,[10,12] although not absolutely required, as pointed out by others.[20] Since the unsymmetrical dimer was the first intermediate formed from **3** and **4**, one can exclude direct carbene dimerization leading to the syn/anti symmetrical dimers. Our ability to observe the stable unsymmetrical dimer enabled us to design more subtle probes to differentiate addition from insertion type reactivity. The sum of the evidence favors nucleophilic addition of the ylide to the thiazolium C2 position, in accord with conclusions based on very different types of experimental evidence.[6,7] The mechanistic probes developed to test the reactivity of the *N*-methyl compound suggest that prior reports invoking a carbene mechanism in similar azolium systems be reevaluated.

The rearrangement of dimers formed from *N*-benzyl- and *N*-[(4-amino-2-methyl-5-pyrimidinyl)methyl] [that is, thiamin] thiazolium compounds on deprotonation is an interesting observation,[10,11] but is irrelevant to the enzyme mechanism, given that the protein is unlikely to allow two thiamin cofactors to come anywhere near each other.

Finally, recent reports on the isolation and characterization of the putative "thiamin ylide" need to be addressed.[9] In experiments performed over several years, with several preparations of **3** and **4**, and subjecting them to a variety of strong bases in Me_2SO, no spectral evidence for a stable ylide was ever obtained in our laboratory. We believe, that the existence of such a stable "thiamin ylide" must await further confirmation.[25]

Experimental Section

General. ^{13}C NMR experiments were conducted at 50.31 MHz on a Varian XL-200 or at 75 MHz on a GEMINI 300 spectrometer. Samples were prepared in an Atmos-Bag under a stream of He.

Materials. *t*-BuOK (97%) from Aldrich was dried in a desiccator over P_2O_5 under vacuum. The [2-^{13}C]thiazolium salts were dried under high vacuum for 1 week prior to the NMR experiments. ^{13}C-labeled thiourea (enriched 91.2 or 99.9 atom %) was purchased from ICON, Summit, NJ, and was used without further purification. Me_2SO-d_6 was purchased from Merck Sharpe and Dohme Isotopes, Canada.

Sample Preparation for ^{13}C NMR. Solutions were prepared by dissolving the thiazolium compounds in 0.8 mL of Me_2SO-d_6 and adding to it 10-μL aliquots of 1.46 N *t*-BuOK (prepared by dissolving 0.5 g of 97% *t*-BuOK in 3 mL of Me_2SO-d_6). Referencing was against external TMS. Other details are presented in the figure legends.

5-(β-Acetoxyethyl)-2-amino-4-methyl[2-^{13}C]thiazole Hydrochloride (31).[21] To a solution of 0.5 g (6.57 mmol) of [^{13}C]thiourea in 100 mL of ethanol was added 1.54 g (8.66 mmol) of 3-chloro-4-oxopentylethanoate at room temperature. After refluxing for 3 h, the reaction mixture was concentrated and washed with ether (3 × 100 mL), yielding 1.822 g (95%) of **30**: ^1H NMR (200 MHz, D_2O/DSS) δ 4.217 (t, 3 H, J = 6.0 Hz), 2.930 (t, 3 H, J = 6.0 Hz), 2.126 (s, 3 H), 2.062 (s, 3 H); ^{13}C NMR (50 MHz, D_2O/DSS) δ 168.7.

5-(β-Hydroxyethyl)-4-methyl[2-^{13}C]thiazole (32).[21] To 0.5 g (1.7 mmol) of **31** dissolved in 9.6 mL of concd HCl was added slowly 2.9 mL of 1 N $NaNO_2$ (precooled to 0 °C) in an ice–salt bath at −5 °C. After the mixture was stirred for 1 h at 0 °C, 4.2 mL (2.3 mmol) of H_3PO_2 was slowly added, and the mixture was stored at 2 °C for 48 h. Next, the pH of the solution was adjusted slowly to 10 with the addition of 6 N NaOH at −5 °C. After further stirring for 30 min, the solution was extracted with ethyl acetate (5 × 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under vacuum. The residue was flash chromatographed over silica gel, eluting with acetone/hexane (0/10 to 3/7), and yielded 0.149 g (61%) of **32**: ^1H NMR (200 MHz, D_2O/DSS) δ 8.745 (d, 1 H, J = 211.6 Hz), 3.786 (t, 2 H, J = 6.2 Hz), 3.010 (t, 2 H, J = 6.2 Hz), 2.338 (s, 3 H); ^{13}C (50 MHz, D_2O/DSS) δ 151.524 (decoupled) or 153.94 and 149.74 (J = 211.3 Hz).

5-(β-Ethoxyethyl)-4-methyl[2-^{13}C]thiazole (33).[22] To a solution of 0.14 g (1.09 mmol) of **32** in 6 mL of dry THF was slowly added NaH (60%, 0.05 g, 1.25 mmol) in a dry ice–acetone bath. The reaction mixture was allowed to warm to room temperature and was stirred for a further 20 min. The mixture was cooled to 0 °C, and bromoethane (0.1 mL, 1.34 mmol) was slowly added to it. Stirring was continued for another 1 h at room temperature, 5 mL of water was added, and the mixture was extracted with methylene chloride (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was flash chromatographed over silica gel, eluting with acetone–hexane (0–10%) and yielded 0.144 g (92%) of **33**: ^1H NMR (200 MHz, $CDCl_3$/TMS) δ 8.554 (d, 1 H, J = 209.7), 3.451–3.620 (m, 4 H), 3.007 (t, 2 H, J = 6.6 Hz), 2.396 (s, 3 H), 1.208 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$/TMS) δ 151.624 (decoupled).

3-Benzyl-5-(β-ethoxyethyl)-4-methyl[2-^{13}C]thiazolium Bromide (4). To a solution of 0.144 g (0.92 mmol) of **33** in 5 mL of 1-butanol was added 0.2 mL of benzyl bromide (1.68 mmol), and the reaction was run with stirring at 110 °C for 10 min. After cooling, the solution was concentrated, and the residue was washed with ethyl acetate (3 × 5 mL) while sonicating to yield 0.268 g (82%) of **4**: mp 84–85 °C; ^1H NMR (200 MHz, $CDCl_3$/TMS) δ 11.513 (d, 1 H, J = 214.9 Hz), 7.353 (m, 5 H), 6.126 (d, 2 H, J = 5.2 Hz), 3.488–3.645 (m, 4 H), 3.013 (t, 2 H, J = 5.4 Hz), 2.421 (s, 3 H), 1.192 (t, 3 H, J = 7.0 Hz); ^{13}C NMR (50 MHz,

(25) While results here reported in this regard may be considered to constitute "negative evidence" (since the ylide was not observed under any experimental condition used in this laboratory), it is relevant to point out that the proton NMR spectrum attributed to the "thiamin ylide" structure **4** in ref 9d, was virtually the same as that reported by Doughty and assigned to the tricyclic form of thiamin.[10]

Me_2SO/TMS) δ 156.79 (decoupled).

2-Amino-4,5-dimethyl[2-^{13}C]thiazole Hydrochloride (34).[21] To a solution of 0.5 g (6.75 mmol) of [^{13}C]thiourea in 100 mL of ethanol was added 0.746 g (7 mmol) of 3-chlorobutanone at room temperature. After refluxing for 3 h, the solution was concentrated, and the residue was washed with ether (3 × 100 mL), yielding 1.12 g (98%) of **34**: ^{1}H NMR (200 MHz, D_2O/DSS) δ 2.135 (s, 3 H), 2.100 (s, 3 H); ^{13}C NMR (50 MHz, D_2O/DSS) δ 168.5 (decoupled).

4,5-Dimethyl[2-^{13}C]thiazole (35). The procedure was the same as the one outlined for compound **32** above, except 1.1 g (6.3 mmol) of **34** was used, and it yielded 0.51 g of crude **35**, which was used in the next step without purification.

3,4,5-Trimethyl[2-^{13}C]thiazolium Iodide (3·I$^-$). To a solution of 0.51 g of crude **35** from the previous reaction was added excess iodomethane, the flask was sealed, and the reaction mixture was kept in the dark at room temperature for 24 h. Next, the crystals were filtered and washed with dry ethyl acetate (3 × 10 mL) in the sonicator, yielding 0.675 g (2.64 mmol, 42%) of **3·I**.

3,4,5-Trimethyl[2-^{13}C]thiazolium Nitrate (3·NO_3^-). Compound **3·I** dissolved in 2 mL of water was applied to a 200-mL volume column of Dowex AG 3×4A (pretreated with three volumes of distilled water, then with three volumes of 0.005 N HNO_3), and eluted with one volume of 0.005 N HNO_3. The solution was concentrated to dryness, and the residue was chromatographed on silica gel and eluted with acetonitrile, yielding 0.49 g (98%) of **3·NO_3^-**: ^{1}H NMR (200 MHz, Me_2SO-d_6/TMS) δ 9.903 (d, 1 H, J = 218.4 Hz), 4.046 (d, 3 H, J = 2.7 Hz), 2.469 (s, 3 H), 2.376 (s, 3 H); ^{13}C NMR (50 MHz, Me_2SO-d_6/TMS) δ 155.21 (decoupled).

General Procedure for the Reaction of Thiazoles with Alkenyl Bromides. To a solution of 4-methylthiazole (1.0 mL, 11.1 mmol) or 96% benzothiazole (1.2 mL, 11.1 mmol) in dry 1-butanol (0.2 mL) was added alkenyl bromide (1.57 mL, 15 mmol) at 110 °C. After stirring for 3 h, the solution was cooled to room temperature. Ten milliliters of dry hexane was added to the solution, and a gummy product formed. After the solvent was decanted, the gum was sonicated and washed with dry ethyl acetate (2 × 20 mL). The gum was dried in a high vacuum to give essentially pure product, which was then recrystallized from methylene chloride.

3-(3-Butenyl)-4-methylthiazolium Bromide (15). This hyroscopic compound was obtained from the reaction of 4-bromo-1-butene with 4-methylthiazole and gave an 85.5% yield of product (2.22 g): mp 76–77 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS) δ 10.117 (d, 1 H, J = 2.49), 8.041 (s, 1 H), 5.907–5.769 (m, 2 H), 4.573 (t, 2 H, J = 7.0 Hz), 2.626 (q, 2 H, J = 7.10 Hz), 2.585 (s, 3 H); mass spectrum (CI) m/z (relative intensity) 154.0 (54.65), 152.0 (30.20), 100.0 (20.53), 99 (49.04), 72.0 (46.95), 71.0 (46.03), 55.1 (100), 45.0 (25.37), 38.8 (30.46). Anal. Calcd for $C_8H_{12}NSBR·0.5H_2O$: C, 39.60; H, 5.4; N, 5.77. Found: C, 39.55; H, 5.18; N, 5.74.

4-Methyl-3-(pent-4-enyl)thiazolium Bromide (16). This hygroscopic compound was obtained from the reaction of 5-bromo-1-pentene with 4-methylthiazole and gave an 84.3% yield of product (2.32 g): mp 49–50 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS) δ 10.170 (d, 1 h, J = 2.6 Hz), 8.046 (d, 1 H, J = 1.8 Hz), 5.909–5.775 (m, 1 H), 5.128–5.018 (m, 2 H), 4.457 (t, 2 H, J = 7.6 Hz), 2.569 (s, 3 H), 2.126 (q, 2 H, J = 7.6 Hz), 1.997–1.922 (m, 2 H); MS (FAB) m/z (relative intensity) 168.9 (MH^+, 12.44), 167.9 (100.0), 153.9 (18.64), 135.9 (14.07). Anal. Calcd for $C_9H_{14}NSBr·0.3H_2O$: C, 42.68; H, 5.80; N, 5.53. Found: C, 42.45; H, 5.86; N, 5.60.

4-Methyl-3-(pent-4-enyl)benzothiazolium Bromide (17). This compound was obtained from the reaction of 5-bromo-1-pentene with benzothiazole and gave a 63.2% yield of product (2.00 g): mp 111–112 °C; ^{1}H NMR (300 MHz, DMSO-d_6/TMS) δ 10.628 (s, 1 H), 8.546 (d, 1 H, J = 8.1 Hz), 8.457 (d, 1 H, J = 8.1 Hz), 7.970 (t, 1 H, J = 7.3 Hz), 7.884 (t, 1 H, J = 7.3 Hz), 5.905–5.773 (m, 1 H), 5.097–4.994 (m, 2 H), 4.868 (t, 2 H, J = 7.3 Hz), 2.212–2.040 (m, 4 H); MS (CI/isobutane) m/z (relative intensity) 205 (MH^+, 16.1), 204 (40), 145 (8.2), 137 (14.9), 136 (100), 127 (9.1). Anal. Calcd for $C_{12}H_{14}NSBr$: C, 50.71; H, 4.96; N, 4.93. Found: C, 50.40; H, 4.93; N, 5.05.

3,4,5-Trimethylthiazolium Iodide (36·I). To a solution of 4,5-dimethylthiazole (2.0 g, 0.0177 mol) was added excess iodomethane, the flask was sealed, and the reaction mixture was kept in the dark at room temperature for 24 h. Next, the crystals were collected by filtration and washed with dry ethyl acetate (3 × 20 mL) in the sonicator, yielding 4.43 g (0.0176 mol, 98.2%) of **36·I**.

3,4,5-Trimethylthiazolium Chloride (36·Cl). The procedure was the same as the one outlined for 4 above, except 0.005 N HCl was used instead of 0.005 N HNO_3. Compound **36·I** (4.42 g, 0.0173 mol) was used to produce 2.84 g **36·Cl** (0.0167 mol, 96%): ^{1}H NMR (300 NMR, DMSO-d_6/TMS) δ 10.110 (s, 1 H), 4.109 (s, 3 H), 2.502 (s, 3 H), 2.415 (s, 3 H); mass spectrum (FAB), m/z (relative intensity) 128 (MH^+, 8.43), 127 (13.75), 114 (8.12), 113 (100), 85.9 (42.1), 84.9 (30.99), 73.0 (11.17), 72.0 (8.71), 71.0 (90.30), 59.0 (18.84), 50.0 (42.60), 45.0 (25.73).

3,4,5-Trimethyl[2-^{2}H]thiazolium Chloride (37).[6] Compound **36·Cl** (0.5 g, 3.06 mmol) in D_2O (10 mL, 99.9% D) was refluxed for 30 min under a stream of dry N_2. The solution was cooled to room temperature, then concentrated under high vacuum at 30 °C. After the procedure was repeated three times, the solution was concentrated to dryness to yield 0.498 g of **37** (3.03 mmol, 99%): ^{1}H NMR (300 MHz, DMSO-d_6/TMS) δ 4.109 (s, 3 H), 2.502 (s, 3 H), 2.414 (s, 3 H).

3,4,5-Trimethyl[2-^{2}H][2-^{13}C]thiazolium Nitrate (38).[6] The procedure was the same as the one used to synthesize **37**. Compound **3** (20 mg, 0.105 mmol) was used to produce 20 mg of **38** (0.104 mmol, 99.5%): ^{1}H NMR (300 MHz, DMSO-d_6/TMS) δ 4.086 (d, 3 H, J = 4.7 Hz), 2.501 (s, 3 H), 2.409 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6/TMS, broad band proton decoupled) C2-D at δ 155.478 (t, 1 C, J = 33.5 Hz).

3-Methylbenzothiazolium Iodide (24).[23] The procedure was the same as the one outlined for **36·I**. Benzothiazole (1.0 g, 7.4 mmol) was used to produce 2.03 g of **24** (7.34 mmol, 99.2%): mp 220–221 °C; ^{1}H NMR (200 MHz, DMSO-d_6/TMS) δ 10.553 (s, 1 H), 8.535 (d, 1 H, J = 7.9 Hz), 8.345 (d, 1 H, J = 7.9 Hz), 7.975 (t, 1 H, J = 7.0 Hz), 7.913 (t, 1 H, J = 7.3 Hz), 4.421 (s, 3 H).

3-Benzyl-4,5-dimethylthiazolium Bromide (39). To a solution of 4,5-dimethylthiazole (0.5 g, 4.42 mmol) in dry 1-butanol (0.5 mL) was added benzyl bromide (1.13 g, 6.63 mmol) at 110 °C. After being stirred for 10 min, the reaction was cooled to room temperature. On addition of ethyl acetate (3 × 20 mL) to the solution, the product precipitated, yielding 1.17 g (4.02 mmol, 91.0%) of **38**: ^{1}H NMR (300 MHz, DMSO-d_6/TMS) δ 7.492–7.324 (m, 5 H), 5.809 (s, 2 H), 2.499 (s, 3 H), 2.327 (s, 3 H); MS (CI) m/z (relative intensity) 204 (M, 13.6), 171 (8), 142 (10.4), 114 (72.8), 91 (100).

Molecular mechanics calculations were performed with the Sybil software provided by Tripos Associates, St. Louis, MO, on an Evans and Sutherland PS 330 terminal employing Allinger's XMAXIMIN program.[24]

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Registry No. **3·I$^-$**, 134486-68-3; **3·NO_3^-**, 134486-70-7; **4**, 134486-71-8; **15**, 134486-72-9; **16**, 134486-73-0; **17**, 134486-74-1; **21**, 134486-75-2; **22**, 134486-76-3; **23**, 134486-77-4; **24**, 2786-31-4; **25**, 134486-78-5; *syn*-**27**, 134486-79-6; *anti*-**27**, 134486-80-9; *syn*-**29**, 134486-81-0; *anti*-**29**, 134528-84-0; **31**, 134486-82-1; **32**, 134486-83-2; **33**, 134486-84-3; **34**, 134486-85-4; **35**, 134486-86-5; **36·I**, 62993-85-5; **36·Cl**, 134486-87-6; **37**, 134486-88-7; **38**, 134486-90-1; **39**, 28048-27-3; [^{13}C]thiourea, 113899-66-4; 3-chloro-4-oxopentyl ethanoate, 13051-49-5; 3-chlorobutanone, 4091-39-8; 4-methylthiazole, 693-95-8; benzothiazole, 95-16-9; 4-bromo-1-butene, 5162-44-7; 5-bromo-1-pentene, 1119-51-3; 4,5-dimethylthiazole, 3581-91-7.