Ring Transformation Equilibrium (Bond Switch) in the 5-(2-Aminovinyl)isothiazole System via Hypervalent Sulfurane. Synthesis, Structure Determination, and Kinetic Study

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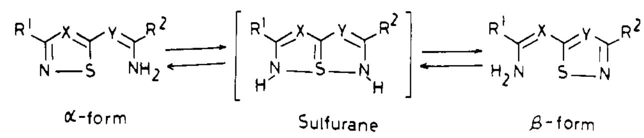
Abstract: Reaction of 3-aryl-5-methylisothiazoles (**4**) with aromatic nitriles afforded the adducts **3**, 5-(2-amino-2-arylvinyl)-3-arylisothiazole derivatives, in the presence of LDA. By employing *p*-chlorobenzonitrile-^{15}N, the presence of ring transformation from one isothiazole (α form) to another isothiazole (β form) was verified. By spectral analyses of **3** compared with 5-[2-(silylamino)-2-arylvinyl]-3-arylisothiazole (**13**-*Z*), **3** was concluded to have trans geometry (**3**-*Z*) with respect to two aromatic rings to arrange N—S···N linearly. The pure α isomers of ^{15}N-labeled **3d** (**3d***-α-*Z*: $Ar^1 = Ar^2 = p\text{-}ClC_6H_4$), **3b** ($Ar^1 = p\text{-}ClC_6H_4$, $Ar^2 = p\text{-}MeC_6H_4$), and **3e** ($Ar^1 = p\text{-}ClC_6H_4$, $Ar^2 = 3,5\text{-}Cl_2C_6H_3$) were synthesized by desilylation of **13b**, **13d***, and **13e**-*Z* and the equilibrium between α form and β form has been shown to take place in neutral solutions. A kinetic study of the rate of equilibration of **3**, which shows the movement of the central sulfur atom along the N–S^{IV}–N line, was performed in benzene-d_6 and Me_2SO-d_6 solution. For example, kinetic parameters for **3d*** in benzene-d_6 are as follows: $\Delta G^{\ddagger}_{298} = 24.4 \pm 0.8$, $\Delta H^{\ddagger} = 12.2 \pm 0.2$ kcal mol^{-1}, $\Delta S^{\ddagger} = -41.0 \pm 0.5$ eu, $k_{298} = 6.21 \times 10^{-6}$ s^{-1}. The rate is greatly accelerated with an added acid or base catalyst. In order to account for the equilibration in neutral solution, a symmetrical hypervalent sulfurane analogous to thiathiophthene is invoked as a key intermediate, which is generated via 1,5-sigmatropic shift of hydrogens.

The weak and electron-rich nature of three-center four-electron bond (hypervalent bond)[1] has attracted much attention recently and hypervalent molecules of typical elements of the second row and below have been synthesized extensively mainly by J. C. Martin's group.[2a] They have shown that the hypervalent bond can be polarized by the difference of the two electron-withdrawing apical groups.[2b] Indeed, bond lengths of S(1)–S(6a) and S-(6a)–S(6) of thiathiophthenes, so-called no bond resonance compounds, are not equal and differ at most by 0.3 Å in crystals, depending on the substituents on the molecular frame.[3] Lability of these bonds has been shown experimentally by us and also by D. H. Reid et al.[4]

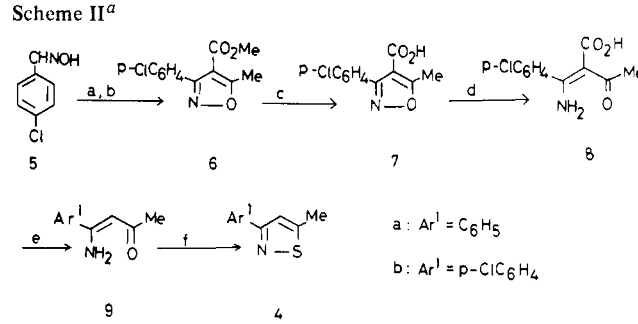
Many examples of bond switching at hypervalent sulfurane have been accumulated for 1,3-dipolar cycloaddition of 1,2-dithiol-3-thiones, iminothiazolines, and so on with activated acetylenes[5] and nitriles.[6] In these reactions, unsymmetrical sulfuranes are commonly invoked as intermediates or transition state. Hence, degenerate rearrangement of heterocycles is expected to take place, in cases where a symmetrical sulfurane could take part as an intermediate.

Scheme I



1 : X = N, Y = N 2 : X = CH, Y = N 3 : X = CH, Y = CH

Scheme II[a]



[a] (a) NBS, DMF; (b) $MeCOCHNaCO_2Me$, DMF; (c) KOH, aqueous EtOH; (d) H_2, Raney Ni, aqueous NaOH; (e) heated at 140 °C; (f) P_4S_{10}, $NaHCO_3$, chloranil, THF.

We have recently communicated such an example employing a thiadiazole system (**1**)[7] and also reported ring transformation from isothiazole to thiadiazole **2** due to the difference of stability in the heteroaromatics.[8] However, X-ray crystallographic analysis of an example of **1**, i.e., 5-[(1-aminoethylidene)amino]-3-(chloromethyl)-1,2,4-thiadiazole, shows that N–S···N atoms are not linearly arranged and the amidino group is rotated to form an intramolecular hydrogen bond to N(4) of the thiadiazole ring.[9]

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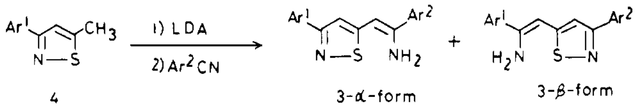
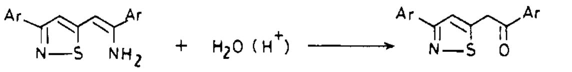
Scheme III



4 3-α-form 3-β-form

a, $Ar^1 = C_6H_5$, $Ar^2 = C_6H_5$; b, $Ar^1 = p\text{-}ClC_6H_4$, $Ar^2 = p\text{-}MeC_6H_4$; c, $Ar^1 = p\text{-}ClC_6H_4$, $Ar^2 = p\text{-}FC_6H_4$; d, $Ar^1 = p\text{-}ClC_6H_4$, $Ar^2 = p\text{-}ClC_6H_4$; e, $Ar^1 = p\text{-}ClC_6H_4$, $Ar^2 = 3,5\text{-}Cl_2C_6H_3$; f, $Ar^1 = p\text{-}ClC_6H_4$, $Ar^2 = 2,6\text{-}Cl_2C_6H_3$

Scheme IV



3a,d

10a: $Ar = C_6H_5$
10b: $Ar = p\text{-}ClC_6H_4$

In order to avoid this complication and to present an ideal system for reversible ring transformation via a hypervalent sulfurane, we now report the preparation and structure determination of 5-(2-amino-2-arylvinyl)-3-arylisothiazoles (3) and also the synthesis of pure α form of 3 and the kinetics of equilibration between α form and β form (Scheme I).

Results

Synthesis of 5-(2-Amino-2-arylvinyl)-3-arylisothiazoles (3). 3-Aryl-5-methylisothiazoles (4) were prepared by suitable modification of the known procedure.[10] The reaction of *p*-chlorobenzaldoxime (5) with *N*-bromosuccinimide in *N,N*-dimethylformamide followed by addition of methyl sodioacetoacetate afforded isoxazole derivative 6 in one-pot procedure. Saponification of 6 gave 4-carboxyisoxazole 7 in 49% overall yield from 5. Hydrogenation of 7 on Raney nickel furnished a mixture of 8 and 9b. The mixture was decarboxylated by heating at 140 °C to produce enamine ketone 9b in 81% yield from 7. The other enamine ketone 9a was prepared by reaction of 1-phenyl-3-ethoxy-2-buten-1-one with hydroxylamine followed by hydrogenation.[11] Sulfurization of 9a with phosphorus pentasulfide, followed by oxidation under reported conditions, produced 4a only in poor yield. Fortunately, sulfurization of 9 with the same reagent under basic conditions (in the presence of sodium hydrogen carbonate in tetrahydrofuran)[12] followed by oxidation with chloranil gave 4 in moderate yield (Scheme II).

The isothiazoles 4 were converted to 5-(2-amino-2-arylvinyl)-3-arylisothiazoles (3) by suitable modification of the procedure developed by Kashima et al. for the preparation of the oxygen analogue 11.[13] Each lithio derivative of 4 was treated with the corresponding aromatic nitriles to give the adducts 3. As the adducts 3 are enamines, they are rather labile for usual handling and especially so under acidic conditions. The parent adduct 3a was too unstable to be purified by preparative TLC or recrystallization, but the vinyl proton at δ 5.93 (s) and the amino proton at δ 4.4 (br s) were observed in the ^1H NMR spectrum ($CDCl_3$) of the crude sample. On the other hand, satisfactory spectral data were obtained for each 3 with a *p*-chlorophenyl group as Ar^1 due to their considerable stability as compared with 3a (Scheme III).

The structural assignment of 3 was made based on the following. The symmetrical adducts **3a,d** were hydrolyzed under acidic conditions to give the corresponding 5-phenacylisothiazoles (**10**) in moderate yields (Scheme IV).

In the ^1H NMR spectrum of **3d**, the vinyl proton appears as a singlet with a chemical shift of δ 5.90 and the heterocyclic proton does also as a singlet of δ 7.30 along with other signals ($CDCl_3$).

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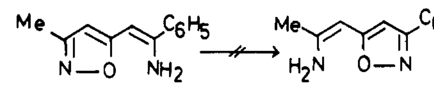
Table I. Equilibrium Ratio in the Bond Switch of **3b–f**[a]

compd	Ar^2	^1H NMR (δ) for vinyl proton: α form	β form	α/β	solvent (35 °C)
3b	$p\text{-}MeC_6H_4$	5.83	5.66	58:42	C_6D_6
		5.93	5.91		$CDCl_3$
3c	$p\text{-}FC_6H_4$	5.87	5.84	52:48	$CDCl_3$
3d	$p\text{-}ClC_6H_4$	5.62	5.62	50:50	C_6D_6
		5.90	5.90		$CDCl_3$
3e	$3,5\text{-}Cl_2C_6H_3$	5.44	5.58	47:53	C_6D_6
		5.90	5.74		DMSO-d_6
3f	$2,6\text{-}Cl_2C_6H_3$	5.60	6.10	47:53	$CDCl_3$

[a] $Ar^1 = p\text{-}ClC_6H_4$.

Scheme V



11 11'

The ^1H NMR spectrum of **3d** in $Me_2SO\text{-}d_6$ was almost unchanged up to 100 °C. On the other hand, it was a pleasant surprise to see that a pair of singlets was observed for the vinyl protons of the unsymmetrical adduct **3e** at δ 5.73 and 5.88 ($Me_2SO\text{-}d_6$), although the heterocyclic protons were buried in the aromatic region. The same phenomena were also observed in solutions for other 3 as shown in Table I, indicating that the unsymmetrical adducts consist of a mixture of two isomers. They are considered to be the normal adduct **3-α** and its ring-transformed isomer **3-β** rather than geometric isomers about the double bond because there was observed only a singlet of vinyl proton for symmetrical adducts **3a,d** in the ^1H NMR spectrum.

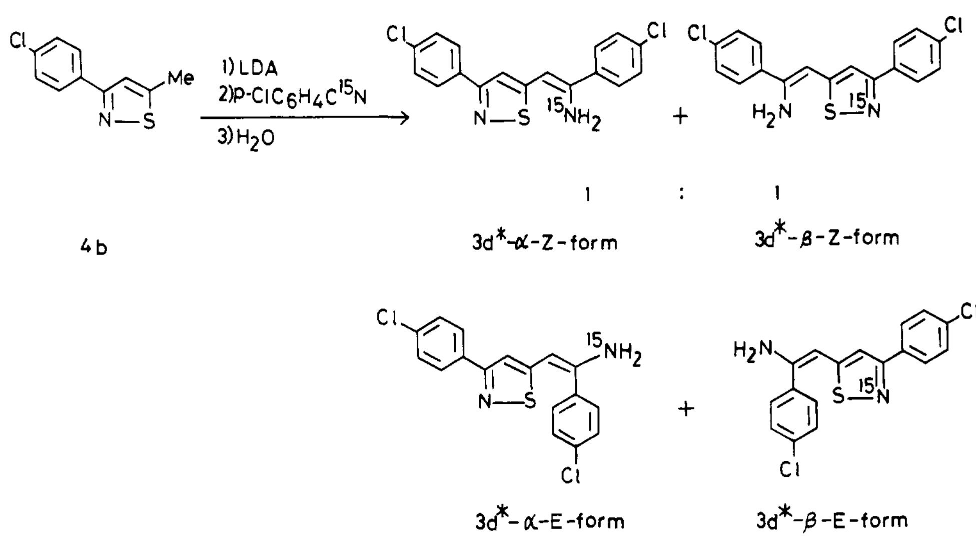
It is not possible in this situation to determine which vinyl proton belongs to α form or β form, but it was firmly done by the synthesis of pure α form of 3 as described later. The ratio is close to unity for every compound but there is a definite trend that the equilibrium is shifted slightly to β form when a more electronegative aryl group relative to the *p*-chlorophenyl group can conjugate with the isothiazole ring. Although chemical shifts of some protons apparently shift according to solvents, the ratios remain almost constant in $CDCl_3$, C_6D_6, and $Me_2SO\text{-}d_6$ and also for the temperature range 30–50 °C. This fact is in contrast to the result of 5-[(aminomethylene)amino]-1,2,4-thiadiazole system which suffers considerable effects by these external changes.[7] It can be understood, however, on the basis of the feature that the present system bears two aromatic rings so that the ratio of the two forms is determined mainly by the conjugation with them.

Judging from the fact that 5-(2-aminovinyl)isoxazole derivative **11** does not show any ring transformation,[13] the occurrence of the bond switch in 3 should certainly be facilitated by participation of the hypervalent sulfuranes[4-6] and this point is further elaborated (Scheme V).

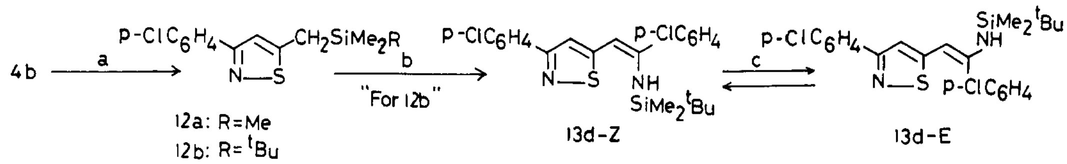
Confirmation of Ring Transformation in 3 by means of ^{15}N-Scrambling Experiment. Treatment of 3-(*p*-chlorophenyl)-5-methylisothiazole (**4b**) with ^{15}N-labeled *p*-chlorobenzonitrile afforded ^{15}N-labeled 5-[2-amino-2-(*p*-chlorophenyl)vinyl]-3-(*p*-chlorophenyl)isothiazole (**3d***). The mass spectrum of **3d*** demonstrated that the level of enrichment was more than 97% but could not indicate which nitrogen in **3d*** was labeled. The ^{15}N scrambling was clarified on the basis of the NMR spectral data. The ^1H and ^{15}N NMR spectra of **3d*** are shown in Figure 1.

In the ^1H NMR spectrum (Figure 1a), the $^{15}NH_2$ protons are seen as a doublet ($^1J_{^{15}NH}$ = 89 Hz) at δ 3.45 together with a broadened singlet for the $^{14}NH_2$ protons at δ 3.4, the integral ratio being 1:1. In the proton-decoupled ^{13}C NMR spectrum, there are two kinds of carbon that couple with ^{15}N, one at δ 133.2 ($^1J_{^{13}C^{15}N}$ = 6.9 Hz, C_3) and the other at δ 145.5 ($^1J_{^{13}C^{15}N}$ = 11.7 Hz, $C_{2'}$). Furthermore, the ring transformation was definitely confirmed by an examination of the non-proton-decoupled ^{15}N NMR spectrum (Figure 1c), which contains a double triplet

Scheme VI



Scheme VII[a]



[a] (a) (1) LDA, (2) RMe_2SiCl; (b) (1) LDA, (2) p-ClC_6H_4CN, (3) H_2O; (c) $h\nu$ (Pyrex filter) or Δ.

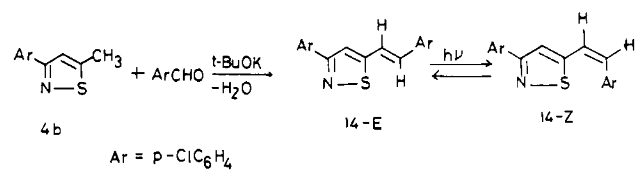
($^3J_{^{15}NH}$ = 4.3 Hz and $^1J_{^{15}NH}$ = 88.9 Hz) at δ 68.7 for the enamino ^{15}N and a singlet at δ 267.6 for the heterocyclic ^{15}N in $CDCl_3$ solution. The assignment of ^{15}N NMR signals is in accordance with resonance signals observed for related nitrogen atoms in the literature.[14] At this point, it is not certain whether the two isomers belong to the *Z* or *E* form (Scheme VI).

Determination of *Z* Geometry of 3 by Spectral Analyses. In order to determine *Z* or *E* geometry of **3**, we tried to synthesize 5-[2-(silylamino)-2-(*p*-chlorophenyl)vinyl]-3-(*p*-chlorophenyl)-isothiazole (**13d**) by coupling of 5-(silylmethyl)isothiazole **12** with *p*-chlorobenzonitrile, which should give **13d** via 1,3-silyl group migration.[15] The silyl group should not appreciably affect the UV spectrum, hence it should be possible to determine the geometry of **3d** by comparisons of the UV spectra of **3d** with *Z* and *E* forms of **13d**, if they could be obtained separately.

Treatment of 3-(*p*-chlorophenyl)-5-methylisothiazole with lithium diisopropylamide (LDA), followed by silylation with trimethyl- or *tert*-butyldimethylsilyl chloride, gave the corresponding 5-(silylmethyl)isothiazole derivatives **12a,b** in good yield. Although the coupling reaction of the trimethylsilyl substrate **12a** with *p*-chlorobenzonitrile afforded only desilylated adduct **3d**, the lithio derivative of **12b** was added to the same nitrile to furnish *N*-silylated product **13d**-*Z* in 61% yield (Scheme VII).

The structural assignment to **13d**-*Z* is based upon the following spectral data and elemental analyses of each isomer. In the ^1H NMR spectrum of **13d**-*Z*, the vinyl proton is seen as a singlet with a chemical shift of δ 5.86 and the heterocyclic proton appears as a singlet at δ 7.32 along with other characteristic signals in $CDCl_3$ solution. When the pure sample **13d**-*Z* in $CDCl_3$ solution was allowed to stand at room temperature for several days, equilibrium was reached between **13d**-*Z* and **13d**-*E*, the ratio being ca. 1:1. Photoisomerization of **13d**-*Z* in ether solution gave a mixture containing 35% of **13d**-*E* by irradiation with a high-pressure mercury lamp through a Pyrex filter. Fractional recrystallization gave **13d**-*E* of ca. 90% purity. The vinyl and heterocyclic protons of **13d**-*E* appear as singlets at δ 6.00 and 6.91 along with other signals. These results indicate that **13d**-*Z* and **13d**-*E* are geometric isomers of each other.

Scheme VIII



Evidence for the geometric assignment to **13d**-*Z* and **13d**-*E* comes from comparison of UV spectra with reference compounds **14**. The reference compound, i.e., 1-isothiazolyl-2-phenylethylene derivative **14**-*E*, was prepared as a single product by aldol-type condensation of **4b** with *p*-chlorobenzaldehyde in the presence of potassium *tert*-butoxide. The *E* isomer is expected to be the main product.[16] Irradiation of **14**-*E* in ether solution with a high-pressure mercury lamp through a Pyrex filter gave a 3:2 mixture with **14**-*Z*. Pure sample of the latter was obtained by TLC separation (Scheme VIII).

The assignment of *E* and *Z* geometry of **14** is easily done on the basis of (i) coupling constant of vinylic protons, **14**-*E*, J = 16.0 Hz, **14**-*Z*, J = 11.7 Hz, and also (ii) UV spectra; the presence of strong absorption at longer wavelength (Figure 2e, λ_{max} = 348 nm, log ε = 4.43) shows the *E* geometry and the presence of a strong band at shorter wavelength (Figure 2d, λ_{max} = 260 nm, log ε = 4.43) along with a shoulder at longer wavelength (λ_{max} = 300 nm, log ε = 4.20) is consistent with the *Z* geometry, which is certified by the well-known result for stilbene.[17] UV spectra of **13d**, **14**, and **3d** are shown in Figure 2. By comparison with spectrum d (**14**-*Z*), spectrum c is assigned to have *E* geometry (**13d**-*E*), hence that of spectrum b should have *Z* geometry (**13d**-*Z*). Characteristic feature of spectrum a for **3d** is almost superimposable on spectrum b, therefore the adduct **3** should have *Z* geometry (two aromatic rings are trans with respect to the double bond).[18]

(14) (a) The reported ^{15}N chemical shifts were evaluated from $^{15}NH_3$ external standard. (b) Rahkamaa, E. *Mol. Phys.* **1970**, *19*, 727. (c) Duthaler, R. O.; Roberts, J. D. *J. Am. Chem. Soc.* **1978**, *100*, 4969.

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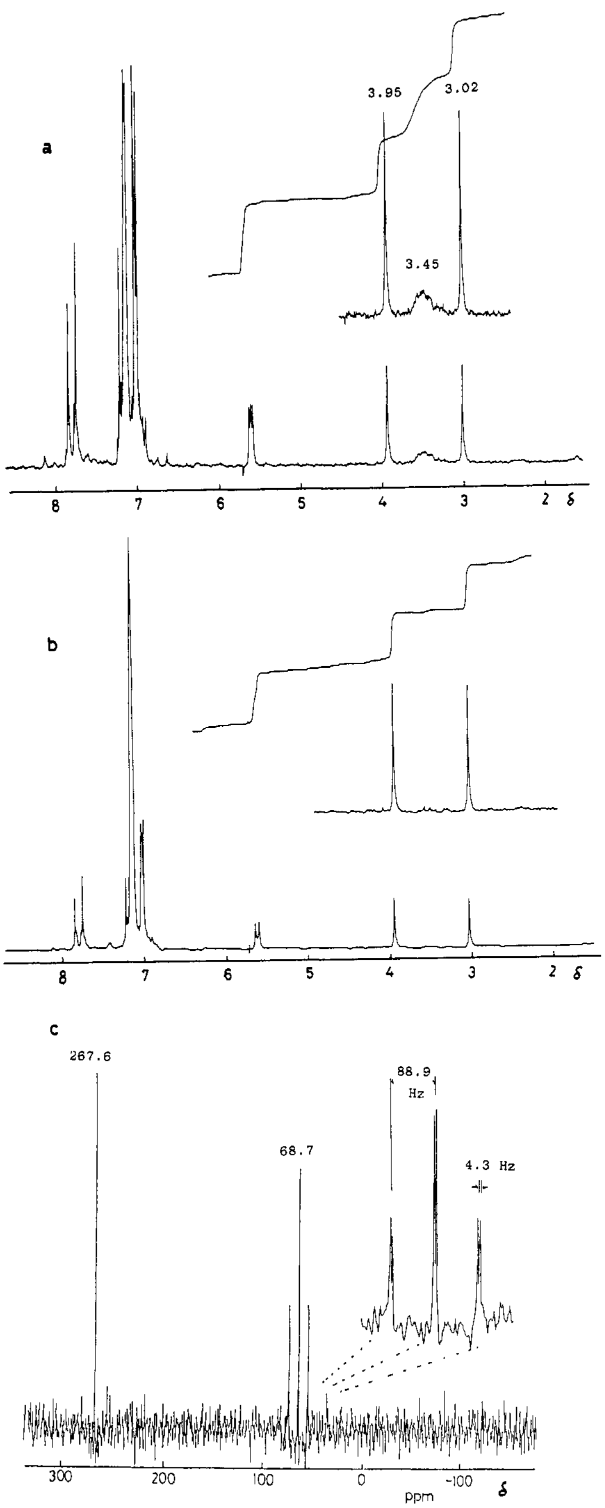


Figure 1. (a) 90-MHz ^{1}H NMR spectrum of **3d*** in benzene-d_6 solution. (b) 90-MHz ^{1}H NMR spectrum of **3d***-α in benzene-d_6 solution. (c) 9.13-MHz ^{15}N NMR spectrum of **3d*** in $CDCl_3$ solution.

Moreover, the observed $^3J_{^{15}NH}$ of 4.3 Hz for the vinyl proton in **3d*** and that of 3.5 Hz for **13d***-*Z* are consistent with the above assignment because $J_{^{15}NH}$ three-bond trans is reported to be 4–6 Hz while cis is 1–2 Hz.[19,28]

(18) X-ray analysis of a single crystal of **3d** was tried, but structure determination has not been successful yet. This may be partly due to a small amount of impurities and also to deterioration of the crystal during the process.
(19) Wasylishen, R.; Schaefer, T. *Can. J. Chem.* **1972**, *50*, 2989.
(20) Preliminary report: Ohkata, K.; Ohyama, Y.; Watanabe, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 4561.

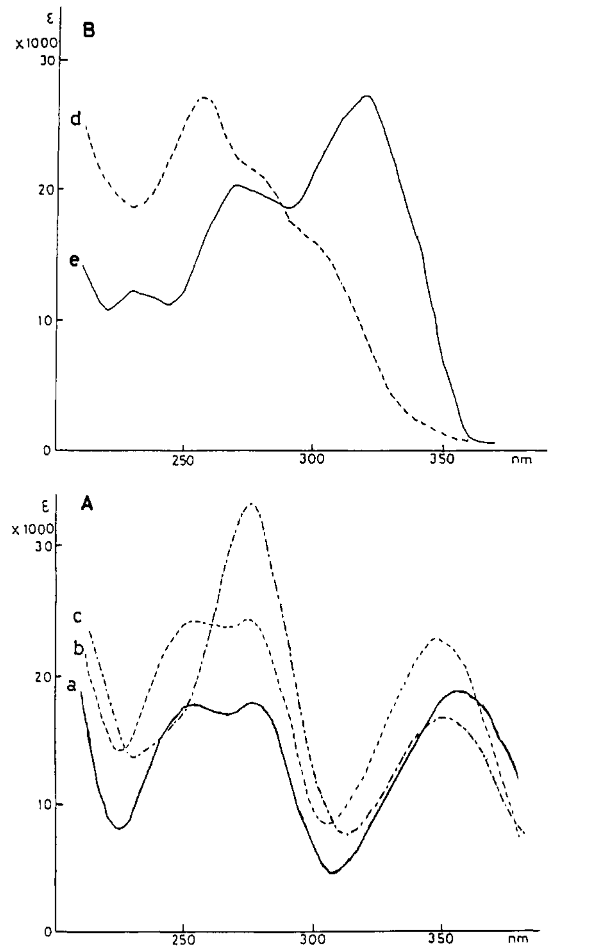
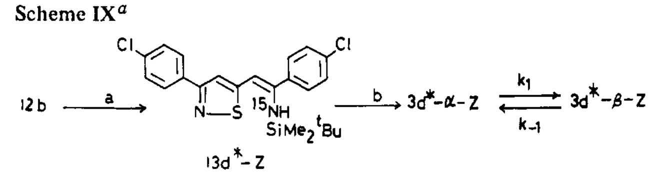


Figure 2. (A) UV spectra of **3d** (a, —), **13d**-*Z* (b, ---), and **13d**-*E* (c, ---) in MeOH. (B) UV spectra of **14**-*Z* (d, ---) and **14**-*E* (e, —) in MeOH.

Scheme IX[a]



[a] (a) (1) *n*-BuLi, (2) *p*-$ClC_6H_4C^{15}N$, (3) H_2O; (b) (1) TBAF, −78 °C, (2) H_2O.

Synthesis of the Pure α Isomer 3-α-Z and Evidence for Equilibration. Although the structure of adduct **3** has been fully

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characterized, it still remains to be scrutinized whether α and β form are produced under the basic conditions during synthesis as shown in Scheme III or there is really equilibration between two isomers under neutral conditions. Here, we describe the conclusive evidence for the latter by preparing pure α-*Z* form of **3b,d*,e** by desilylation of **13b,d*,e**-*Z*.[20]

Labeled **13d***-*Z* was prepared by treatment of **12b** with butyllithium followed by addition of ^{15}N-labeled *p*-chlorobenzonitrile. In the ^{1}H NMR spectrum, the amino proton appears as a characteristic doublet ($^1J_{^{15}NH}$ = 72 Hz) at δ 3.81 and there is not observed any broadened singlet around δ 3.8 assignable to ^{14}NHSi proton. Also, the vinyl proton (δ 5.83, d, $^3J_{^{15}NH}$ = 3.5 Hz), and not the heterocyclic proton, shows a coupling with ^{15}N. Thus, the silyl group shifted exclusively to the nitrogen of the original cyano group and not to the heterocyclic nitrogen. Desilylation of **13d***-*Z* with tetrabutylammonium fluoride (TBAF) at −78 °C in THF afforded pure α-*Z* form of **3d***, when quenched quickly with water at the same temperature with stirring.

In the ^{1}H NMR spectrum of **3d***-α-*Z*, there are the following characteristic signals: δ 4.31 (d, $^1J_{^{15}NH}$ = 89 Hz, 2 H) for the amino proton, 5.88 (d, $^3J_{^{15}NH}$ = 4.3 Hz, 1 H) for the vinyl proton, and 7.33 (s, 1 H) for the heterocyclic proton, together with signals for eight aromatic protons (Figure 1b). It is noteworthy here that the transient amide anion generated by desilylation with the fluoride anion did not cause the ring transformation under the above mentioned conditions.

Heating the benzene-d_6 solution of **3d***-α-*Z* at 50 °C for 50 h resulted in equilibrium to give a 1:1 mixture of **3d***-α-*Z* and **3d***-β-*Z* (Scheme IX). The ^{1}H NMR spectrum was superimposable upon that of **3d*** which was prepared by the direct coupling reaction of **4b** with *p*-chlorobenzonitrile-^{15}*N*. Consequently, the ring transformation equilibrium (bond switch) of **3d** was definitely confirmed.

According to the same procedure described above, the other pure samples (**3b,e**-α) of non-ring-transformed systems were prepared.[20] The ^{1}H NMR spectrum of **3b**-α (Ar^1 = *p*-ClC_6H_4, Ar^2 = *p*-MeC_6H_4) in benzene-d_6 solution shows the following characteristic signals: (i) a singlet of the vinyl proton at δ 5.83 and (ii) lower half (ortho to the isothiazole ring) of AB quartet of the *p*-chlorophenyl group at δ 7.82 (*J* = 8.8 Hz, 2 H) along with other signals. The distinct low-field shift of the two protons of the *p*-chlorophenyl ring reveals that the aromatic ring is conjugated with the isothiazole ring,[8a,21] while four aromatic protons of the *p*-tolyl group appear as a broad singlet at δ 7.3.

Warming the solution to 42 °C for 1 day resulted in equilibrium, affording a mixture of **3b**-α and **3b**-β. Since this equilibration has been proved unambiguously for a symmetric case by employing ^{15}N-labeled **3d***-α, it is easy to assess the ^{1}H NMR signals for **3b**-β by subtraction of those for **3b**-α: (i) a singlet of the vinyl proton at δ 5.66 and (ii) lower half (ortho to the isothiazole ring) of AB quartet of the *p*-tolyl group at δ 8.06 (*J* = 8.1 Hz, 2 H), which supports that the *p*-tolyl ring is conjugated with the isothiazole ring.

By the same procedure, we could assign the chemical shift of the vinyl proton of α and β form for **3e** and assignment for the rest of the unsymmetrical compounds **3c,f** were made by comparison of NMR spectra. The results and equilibrium ratios have been collected in Table I.

Kinetic Studies on the Bond Switching Equilibration. The rates of reversible ring transformation of **3b,d*,e** were measured in benzene-d_6 or Me_2SO-d_6 solutions in the probe of a Hitachi R-90H FT NMR spectrometer. Close attention was paid to standardization by keeping the experimental conditions such as spinning rate, solution volume, concentration, etc. as rigorously identical as possible in all runs. The rates were calculated by using the integral ratio of the vinyl proton of α and β form for **3b** and **3e**, but that of NH_2 and $^{15}NH_2$ for **3d***. Consistent results were obtained by using different probes. The reactions were found to follow nicely to reversible first-order kinetics for more than 3 half-lives in all cases.[22] Typical examples of first-order rate constants (k_1 and k_{-1}) are collected in Table II. Activation parameters were calculated from the Arrhenius plots (e.g., Figure 3), and errors in those values were evaluated from the standard deviation in the plots. The results are shown in Table III, which are standardized for 25 °C.

The reaction constants with an added acid or base as catalyst were also determined in Me_2SO-d_6 solutions, but the data were not as accurate as those in neutral solutions due to the inherent lability of the present substrates toward some acids or bases.

Table II. Kinetic Data for Bond Switch of **3**

compd	solvent	T,[a] °C	10^4k_1, s^{-1} ($\alpha \rightarrow \beta$)	10^4k_{-1}, s^{-1} ($\beta \rightarrow \alpha$)	corr coeff
3b	C_6D_6	56.3	1.95	2.70	0.998
		51.9	1.27	1.75	0.985
		49.1	0.985	1.36	0.993
		42.1	0.707	0.976	0.990
		33.4	0.311	0.429	0.988
3d	C_6D_6	57.2	0.517	0.517	0.995
		45.2	0.251	0.251	0.999
		32.5	0.107	0.107	0.988
3e	C_6D_6	65.5	1.32	1.19	0.996
		64.8	1.06	0.940	0.982
		64.1	0.998	0.885	0.988
		64.0	1.07	0.971	0.989
		53.9	0.594	0.534	0.998
		53.6	0.665	0.601	0.997
		46.5	0.402	0.356	0.988
		46.2	0.434	0.385	0.985
		33.0	0.176	0.159	0.998
		33.0	0.186	0.168	0.991
		33.0	0.193	0.175	0.999
3e	Me_2SO-d_6[b]	66.4	0.346	0.307	0.995
		65.1	0.392	0.348	0.999
		53.4	0.182	0.162	0.999
		53.4	0.175	0.155	0.999
		46.5	0.0937	0.0831	0.986
		46.0	0.1047	0.0928	0.998
		33.0[c]	0.0392	0.0347	
3e	Me_2SO-d_6[b,d]	33.0	5.29	4.69	0.999
3e	Me_2SO-d_6[b,e]	33.0	0.994	0.881	0.970

[a] Temperature was measured at the probe of NMR instrument by using a linear relationship between temperature and the proton chemical shift of ethylene glycol. [b] Rate constants were calculated by using *m* = 0.53 in benzene-d_6 because the signals for the vinyl and amino protons of **3e**-α,β overlapped each other in the ^{1}H NMR spectrum in solution. [c] Extrapolated value based upon the activation parameters. [d] In the presence of 0.3 equiv of pyridinium hydrogen tetrafluoroborate. [e] In the presence of 3 equiv of pyridine.

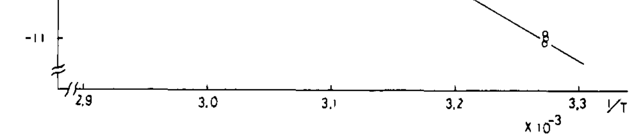

Figure 3. Arrhenius plots for bond switch of **3e** ($\alpha \rightarrow \beta$) in benzene-d_6.

Discussion

Influence of Concentration of Substrate, Acid, and Base. The effect of concentration of **3** was investigated in benzene-d_6 and Me_2SO-d_6 solution: (i) with **3b**-α in benzene-d_6 at 33.5 °C, the rate constant (10^5k_1, s^{-1}) was 3.15 at the molar concentration of 0.065 and 3.11 at 0.033; (ii) with **3e**-α in Me_2SO-d_6 at 53.4 °C,

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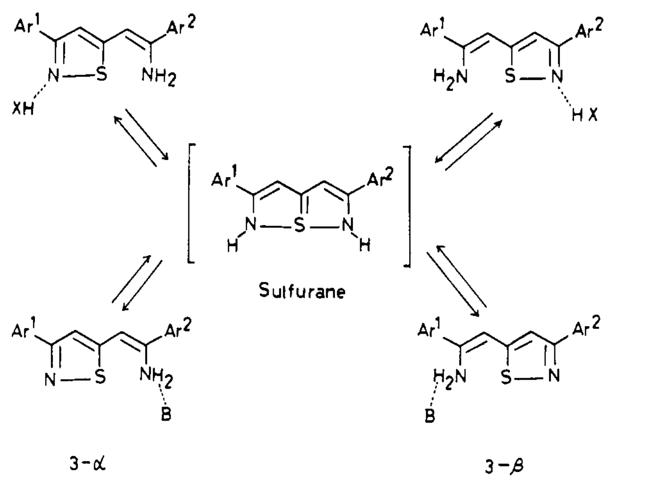
Table III. Activation Parameters and Rate Constants for Bond Switch of **3b,d,e** in Benzene-d_6

	3b		3d	3e[a]	
	$\alpha \xrightarrow{k_1} \beta$	$\beta \xrightarrow{k_{-1}} \alpha$	$\alpha \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \beta$	$\alpha \xrightarrow{k_1} \beta$	$\beta \xrightarrow{k_{-1}} \alpha$
$\Delta H^{\ddagger}{}_{25\,°C}$, kcal/mol	14.7 ± 1.1	14.7 ± 1.1	12.2 ± 0.2	11.0 ± 0.4	10.9 ± 0.4
$\Delta S^{\ddagger}{}_{25\,°C}$, eu	−30.9 ± 3.3	−30.2 ± 3.4	−41.0 ± 0.5	−44.0 ± 1.1	−44.4 ± 1.1
$\Delta G^{\ddagger}{}_{25\,°C}$, kcal/mol	23.9 ± 2.1	23.7 ± 2.1	24.4 ± 0.8	24.1 ± 0.7	24.1 ± 0.7
corr coeff	0.994	0.992	0.999	0.996	0.995
k(25 °C),[b] s^{-1}	1.56×10^{-5}	2.15×10^{-5}	6.21×10^{-6}	1.12×10^{-5}	1.02×10^{-5}

[a] In Me_2SO-d_6, for $\alpha \rightarrow \beta$, $\Delta H^{\ddagger}{}_{25\,°C}$ = 13.6 ± 1.1 kcal/mol, $\Delta S^{\ddagger}{}_{25\,°C}$ = −38.7 ± 3.7 eu, $\Delta G^{\ddagger}{}_{25\,°C}$ = 25.1 ± 2.2 kcal/mol, corr coeff 0.987, and k(25 °C)[b] = 2.09×10^{-6} s^{-1}; for $\beta \rightarrow \alpha$, $\Delta H^{\ddagger}{}_{25\,°C}$ = 13.6 ± 1.1 kcal/mol, $\Delta S^{\ddagger}{}_{25\,°C}$ = −38.9 ± 3.7 eu, $\Delta G^{\ddagger}{}_{25\,°C}$ = 25.2 ± 2.2 kcal/mol, corr coeff 0.987, and k(25 °C)[b] = 1.85×10^{-6} s^{-1}. [b] Extrapolated values based upon the activation parameters.

Scheme X



the rate constant ($10^5 k_1$, s^{-1}) and the molar concentration were as follows, i.e., 1.93, 0.13; 2.02, 0.10; 1.96, 0.099; 1.98, 0.042; (iii) the effect of water was also checked carefully under the above conditions (ii) and it was found negligible within the molar ratio of water to **3e**-α of 0.50–3.00 ($10^5 k_1$ = 1.63–2.02 s^{-1}); (iv) with D_2O instead of H_2O, it was shown that the rate of exchange of the vinyl proton of the enamino group due to enamine–imine tautomerism is several times faster than that of the present equilibration (<10 times); (v) molecular weight determination was carried out by vapor pressure osmometry and it was found that **3** exists as a monomer in benzene solution in a range of molar concentration of 0.005–0.020, i.e., **3b** 340 (calcd, 327), **3d** 343 (347), and **3e** 390 (382). Therefore, it is established that the equilibration of **3**-α takes place unimolecularly and follows the kinetics for a reversible first-order reaction. As the substrate **3** is slightly unstable in the presence of water, and in protic solvents, aprotic solvents were used for further kinetic measurements.

Although the present substrate is not stable enough to obtain accurate reaction rate constants in the presence of an additional acid or base, the reaction of **3e** (0.033 M) was accelerated by a factor of ca. 130 in the presence of pyridinium hydrogen tetrafluoroborate (0.01 M). In addition, the equilibration was rapidly achieved by a factor of ca. 25 in the presence of pyridine (0.1 M) compared with that of neutral conditions as shown in Table II (in Me_2SO).

Since the rate constant for equilibration was not affected by the concentration of the substrate but was enhanced markedly with an additional acid or base, we can assume that under acidic conditions, protonation occurs at the nitrogen of the isothiazole ring to make the N–S bond weaker and allow the sulfur atom to accept an electron pair from the enamino nitrogen. On the other hand, under basic conditions, the assisted deprotonation by an additional base increases the nucleophilicity of the enamino nitrogen to attack the sulfur atom. Even under catalytic conditions, symmetric sulfurane may well take part as an intermediate as shown in Scheme X. Such an acid-catalyzed enhancement of ring-transformation equilibrium has been quantitatively investigated for the 5-[(aminomethylene)amino]-1,2,4-thiadiazole system.[4b] Hence, the mechanism of the equilibration under catalytic conditions should be essentially different from that in neutral solutions.

Influence of Solvents, Substituents, and the Mechanism. The rate of the bond switching equilibration of **3e** at 25 °C in Me_2SO-d_6 was extrapolated to be 2.09×10^{-6} s^{-1} and the activation parameters were calculated to be $\Delta G^{\ddagger}$ = 25.1 ± 2.2 kcal mol^{-1}, $\Delta H^{\ddagger}$ = 13.6 ± 1.1 kcal mol^{-1}, and $\Delta S^{\ddagger}$ = −38.7 ± 3.7 eu for 25 °C. While the corresponding values in benzene-d_6 were 1.12×10^{-5} s^{-1}, 24.1 ± 0.7 kcal mol^{-1}, 11.0 ± 0.4 kcal mol^{-1}, and −44.0 ± 1.1 eu as shown in Table III. Hence, the rate constant is about 5 times as fast as in nonpolar benzene than in polar Me_2SO and the activation enthalpy is considerably smaller (2.6 kcal mol^{-1}) but the activation entropy is larger in negative value. This solvent effect and the unimolecular nature of the present equilibration imply that the reaction proceeds through nonpolar transition state and a couple of sulfuranes can be proposed to effect the transformation including [1,5]-sigmatropic shift of hydrogens as illustrated in Scheme XI. The larger activation enthalpy as well as the less negative activation entropy in Me_2SO can be ascribed to stabilization of the initial state by solvation of the amino group with Me_2SO.[23]

Scheme XI

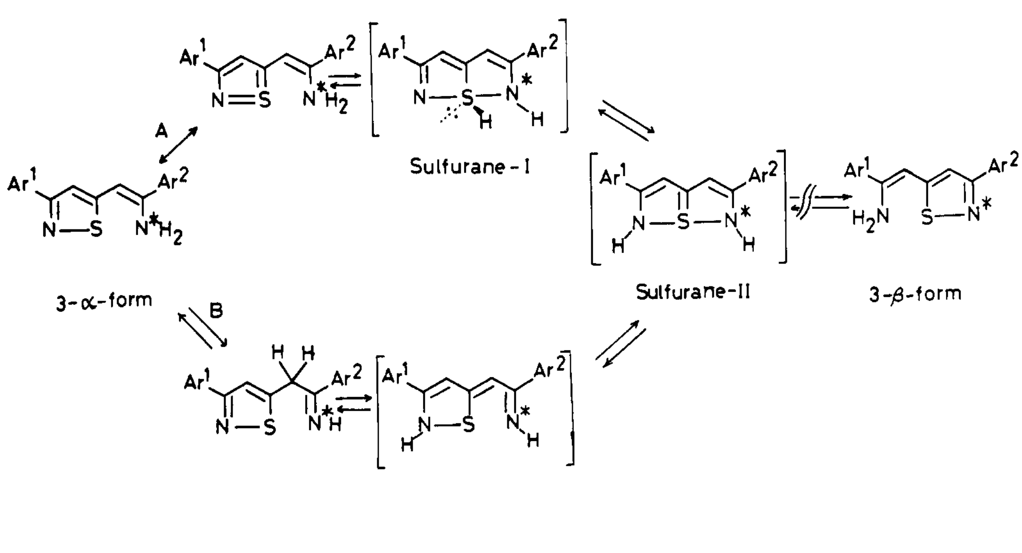
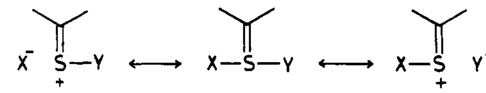


Table IV. Relative Kinetic Values[a] of the Bond Switch of 3b,d,e at 25 °C in Benzene-d_6[b]

		$\alpha \xrightarrow{k_1} \beta$					$\beta \xrightarrow{k_{-1}} \alpha$				
compd	Ar[2]	k_{rel}	$\delta\Delta G^*$, kcal/mol	$\delta\Delta H^*$, kcal/mol	$\delta\Delta S^*$, eu	$\delta T\Delta S^*$, kcal/mol	k_{rel}	$\delta\Delta G^*$, kcal/mol	$\delta\Delta H^*$, kcal/mol	$\delta\Delta S^*$, eu	$\delta T\Delta S^*$, kcal/mol
3b	p-MeC_6H_4	2.51	−0.5	2.5	10	3.0	3.44	−0.7	2.5	11	3.2
3d	p-ClC_6H_4	1.00	0	0	0	0	1.00	0	0	0	0
3e	3,5-$Cl_2C_6H_3$	1.80	−0.3	−1.2	−3	−0.90	1.64	−0.3	−1.3	−3.4	−1.0

[a] δ, difference of kinetic parameters relative to those of **3d**. [b] Ar[1] = p-ClC_6H_4.

Scheme XII



The present scheme is reasonable since it is well established that a reaction which proceeds via polar intermediates starting from a neutral substrate is generally accelerated in more polar solvents. Moreover, the fact is supportive of the above interpretation that the *N,N'*-dimethyl derivative of sulfurane II is stable and the structure was determined by X-ray crystallography, i.e., diazathiapentalene derivative (**16**).[24] We prefer path A where sulfurane I may represent the transition state, although we cannot rule out path B where [1,5]-sigmatropic shift takes place from the imine form of **3**-α. In each path, sulfurane II is invoked as an intermediate.

Therefore, rates were measured in a nonpolar solvent, benzene-d_6, and the results are collected in Table III. Although there is almost no substituent effect on the reaction rate or ΔG^* (see Table III), a dissection of the latter into its ΔH^* and ΔS^* reveals some interesting characteristics, that is, ΔH^* decreases in the order of **3b** > **3c** > **3e** and the absolute value of ΔS^* increases in the reverse order. Therefore, the differences of kinetic parameters for unsymmetrical molecules **3b,e** are calculated using the symmetrical molecule **3d** as a standard (Table IV). On the whole, the general trend is essentially the same regardless of the direction of bond switch ($\alpha \rightarrow \beta$ or $\beta \rightarrow \alpha$) as expected from the equilibrium constants in Table I.

The following points are noticeable from Tables III and IV: (i) the rate constant (k_1) of the symmetrical molecule (**3d**) is the slowest, (ii) the activation entropy (−30 to −44 eu) is very large in negative value for a unimolecular concerted process,[25] (iii) the activation entropy of **3b** is considerably smaller in negative value and this fact overwhelms the effect of larger activation enthalpy for the total equilibration rate.

The relative magnitude of activation entropy suggests that the compound (**3e**) with a more electronegative group relative to p-chlorophenyl group would pass through a tighter transition state and that of activation enthalpy does imply that the transition state of **3e** is the most stable of the three. This is in accord with the well-known general trend that a hypervalent bond is more stabilized with an electronegative group.[1,26] Furthermore, fact (i) is consistent with the general idea that any contribution of ionic structures stabilizes the system (sulfuranes in this case) (Scheme XII).[26]

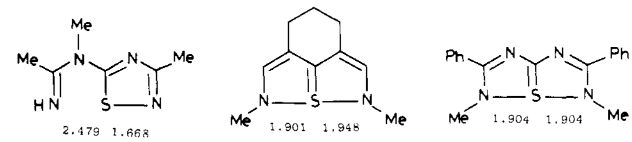
Activation entropies of degenerate sigmatropic rearrangements such as certain Cope rearrangements and the 1,5-sigmatropic shift of hydrogens are in the range of −10 eu.[27] Fact ii shows much larger negative values for the present reversible unimolecular equilibration. The major source of this constraint would stem from the formation of sulfuranes, which necessarily involves the restriction of rotation about the isothiazolyl and the vinyl groups so as to arrange N–S···N atoms linearly and then to contract the molecular frame in order to come up to sulfurane II.

Judging from the coupling constant of $^1J_{^{15}NH}$ (88.9 Hz) of the amino group of **3d**, nitrogen s character of the amino group is calculated to be 32% by using eq 1,[28] which shows that the nitrogen

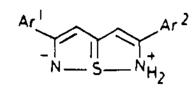
$$\%s = 0.43\,^1J_{^{15}NH} - 6 \qquad (1)$$

has almost exact sp^2 hybridization. Oxidative addition of the N–H bond to sulfur would form sulfurane I which is followed by 1,5-sigmatropic shift of hydrogen to proceed to symmetrical sulfurane II.

Finally we can picture the essence of "bond switch" as the movement of the central sulfur atom along the hypervalent N–S^{IV}–N bond. By referring to the results of X-ray crystallographic analyses of relevant molecules (**15**,[29] **16**,[24] and **17**[30]), the molecular frame of **3** and sulfurane II can be estimated as shown in Scheme XIII. According to the formation of sulfurane I, the total N–S···N distance contracts to 3.80 Å (1.90 + 1.90) starting from 4.17 Å (1.67 + 2.50). The total N–S^{IV}–N length of sulfuranes



15 16 17



18

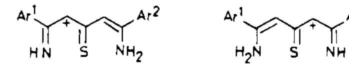
can be assumed to remain constant (3.80 Å) during the movement of the sulfur atom, because the total S–S^{IV}–S length of thiathiophthenes stays at 4.68 ± 0.06 Å where the length of each S–S^{IV} differs at most by 0.30 Å.[3] The central sulfur atom is invoked to move back and forth as a pendulum on the hypervalent bond at least by 0.46 Å starting from sulfurane I formed from **3**-α (1.67 + 2.13) to symmetric sulfurane II (1.90 + 1.90) and moves further to the other sulfurane I (2.13 + 1.67) in order to go to **3**-β according to sigmatropic shift of the hydrogens. The rate of the movement of the sulfur atom in neutral nonpolar solvents is estimated to be around $1 \times 10^{-5}\ s^{-1}$, $\Delta H^* = 12$ kcal mol^{-1}, $\Delta S^* = -40$ eu at 25 °C.

In conclusion, as the rates of equilibration of **3** are accelerated extraordinarily by an added acid or base, the mechanism of the equilibration of neutral molecule **3** should differ from them.[31] We believe that the present transformation is facilitated by contribution of hypervalent sulfurane(s) accompanied by 1,5-sigmatropic shift of hydrogens, and an S_N2-like transition state involving a zwitter ion (**18**) can be ruled out.

Experimental Section

All the melting points are uncorrected. IR spectra were obtained with a Hitachi 215 grating IR spectrophotometer. Electronic spectra were measured on a Hitachi 124 spectrophotometer. ^1H NMR measurements

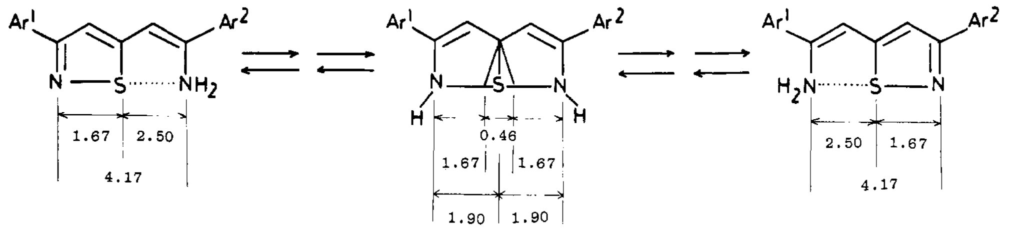
(29) Iwasaki, F.; Akiba, K. *Acta Crystallogr., Sect. B* **1981**, *B37*, 180.
(30) Iwasaki, F.; Akiba, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2581.
(31) One of referees commented that the acid- and base-catalyzed mechanisms may not in fact be associative and the possibility of interconversion of protonated **3** by way of dissociated A and B cannot be ruled out. This may



A B

be one of the possibilities, but the mechanism postulated as Scheme X seems more reasonable, because pK_a of thiazoles and thiadiazoles are measured while keeping the molecular frame intact.

Scheme XIII



3-α-form 3-β-form

were carried out on Varian T-60 and Hitachi R-90H instruments, using tetramethylsilane as the internal reference.

Methyl 3-(*p*-Chlorophenyl)-5-methylisoxazole-4-carboxylate (6). To a solution of *p*-chlorobenzaldoxime (27.9 g, 0.18 mol) in 80 mL of DMF was added a solution of *N*-bromosuccinimide (35.1 g, 0.20 mol) in 70 mL of the same solvent at 10–15 °C. The mixture was stirred for 2 h, followed by treatment with methyl sodioacetoacetate which was prepared from methyl acetoacetate (45.7 g, 0.39 mol) and sodium (9.1 g) in methanol (70 mL). Stirring was continued for 4 h at 0 °C and for 15 h at room temperature. The reaction mixture was diluted with water and continuously extracted with hexane. The organic phase was washed with water, dried, and evaporated to leave a colorless solid (29.5 g, 65%). Recrystallization of the solid from ether–hexane afforded **6**: mp 56–58 °C (lit.[32] 63–64 °C); ^{1}H NMR δ ($CDCl_3$) 2.80 (s, 3 H), 3.78 (s, 3 H), 7.32–7.70 (m, 4 H).

3-(*p*-Chlorophenyl)-5-methylisothiazole-4-carboxylic Acid (7). A mixture of **6** (38.4 g, 0.15 mol) and potassium hydroxide (30 g, 0.54 mol) in aqueous ethanol (350 mL of ethanol and 100 mL of water) was heated under reflux with vigorous stirring for 10 h. After removal of ethanol, the mixture was diluted with water (200 mL) and washed with methylene chloride. The aqueous solution was acidified with 0.1 M hydrochloric acid to afford a colorless solid. Recrystallization of the solid from ethanol gave 27.4 g (75%) of **7**: mp 217–218 °C (lit.[32] mp 213–214 °C); ^{1}H NMR δ (Me_2SO-d_6) 2.72 (s, 3 H), 7.3–7.9 (m, 5 H).

1-Amino-1-(*p*-chlorophenyl)-1-buten-3-one (9b). A mixture of **7** (20 g, 0.082 mol) dissolved in sodium hydroxide solution (NaOH(4 g)/water(200 mL)) and 20 g of Raney nickel (W-2) was stirred under hydrogen atmosphere at room temperature. Slightly excess hydrogen than the theoretical amount was absorbed. After the catalyst was filtered out, the filtrate was acidified to afford a colorless solid. The product consisted of a mixture of 1-amino-1-(*p*-chlorophenyl)-3-oxo-1-buten-2-carboxylic acid (**8**) (7.2 g, 36%) and enamine ketone (**9b**, 8.2 g, 51%). The crude acid **8** was heated at 140 °C for 15 min to give **9b** in 83% yield. Recrystallization of **9b** from benzene afforded pure sample (14 g) as colorless crystals: mp 137–138 °C; IR ν_{max} (KBr) 3300, 3150, 1600, 1530, 1470 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 2.10 (s, 3 H), 5.39 (s, 1 H), 7.20–7.85 (m, 4 H); mass spectrum, *m/e* 195 (M^+), 196 (M^+ + 1), and 197 (M^+ + 2).

Anal. Calcd for $C_{10}H_{10}NOCl$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.66; H, 5.04; N, 7.16.

1-Amino-1-phenyl-1-buten-3-one (9a). 3-Phenyl-5-methylisoxazole was prepared from 1-phenyl-3-ethoxy-2-buten-1-one and hydroxylamine by a previously reported method.[11] The isoxazole was hydrogenated on Raney nickel (W-2) catalyst in ethanol to afford **9a** in 74% yield: mp 85–88 °C (lit.[11] 86–87 C); IR ν_{max} (Nujol) 3300, 3150, 1605, 1530 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 2.15 (s, 3 H), 5.43 (s, 1 H), 7.2–7.7 (m, 5 H).

3-Phenyl-5-methylisothiazole (4a). To a mixture of **9a** (2.00 g, 12.4 mmol) and sodium hydrogen carbonate (2.00 g, 12.4 mmol) in 50 mL of dry THF was added phosphorus pentasulfide (1.65 g, 3.72 mmol) in one portion at room temperature. After 15 h of stirring, chloranil (1.80 g, 7.20 mmol) was added and then the mixture was stirred for 12 h. The reaction mixture was diluted with ether and filtered. The filtrate was washed with sodium hydrogen carbonate solution, dried, and evaporated. Chromatography of the residue on silica gel followed by sublimation of the elute gave 1.31 g (60%) of **4a** as a colorless solid. Recrystallization from hexane afforded pure sample of **4a**: mp 55–57 °C (lit.[17] mp 49–51 °C); ^{1}H NMR δ ($CDCl_3$) 2.62 (d, *J* = 1 Hz, 3 H), 7.2–7.6 (m, 4 H), 7.8–8.2 (m, 2 H).

3-(*p*-Chlorophenyl)-5-methylisothiazole (4b). By a method similar to that used for **4a**, **4b** (6.55 g, 53%) was obtained from **9b** (11.46 g, 58.6 mmol), phosphorus pentasulfide (9.13 g, 20.6 mmol), sodium hydrogen carbonate (19.24 g, 0.229 mol), and chloranil (9.5 g, 38.6 mmol) in 300 mL of THF. Recrystallization of the product from hexane gave colorless crystals of **4b**: mp 89–90 °C; IR ν_{max} (KBr) 1530, 1490, 1420 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 2.61 (d, *J* = 1 Hz, 3 H), 7.25 (q, *J* = 1 Hz, 1 H), 7.35, 7.81 (ABq, *J* = 8 Hz, 4 H); mass spectrum, *m/e* 209 (M^+), 210 (M^+ + 1), 211 (M^+ + 2).

Anal. Calcd for $C_{10}H_8NSCl$: C, 57.28; H, 3.85; N, 6.68. Found: C, 57.41; H, 3.71; N, 6.59.

Synthesis of 5-(2-Aminovinyl)isothiazoles 3. General Procedure. 3-(*p*-Chlorophenyl)-5-[2-amino-2-(*p*-chlorophenyl)vinyl]isothiazole (3d). To a solution of lithium diisopropylamide, prepared from *n*-butyllithium (1.65 mL of 1.6 M hexane solution) and diisopropylamine (0.37 mL, 2.6 mmol) in 30 mL of dry THF, was added a solution of **4b** (500 mg, 2.4 mmol) in the same solvent (10 mL) at −78 °C. After 30 min of stirring, *p*-chlorobenzonitrile (360 mg, 2.6 mmol) in 10 mL of THF was introduced into the reaction mixture at −78 °C. The mixture was stirred at the same temperature for 3 h and at room temperature for 15 h. The mixture was poured onto ice and the product was extracted into ether. The combined organic layers were washed with water, dried, and evaporated to yield a yellow solid. Trituration with ether–hexane afforded 470 mg (56%) of **3d** as a colorless solid: mp 138–141 °C; IR ν_{max} (KBr) 3450 cm^{-1}; UV λ_{max} (log ε, MeOH) 255 (4.25), 356 nm (4.28); ^{1}H NMR δ ($CDCl_3$) 4.13–4.60 (br s, 2 H), 5.90 (s, 1 H), 7.30 (s, 1 H), 7.43 (s, 4 H), 7.33, 7.83 (ABq, *J* = 9 Hz, 4 H).

Anal. Calcd for $C_{17}H_{12}N_2SCl_2$: C, 58.80; H, 3.48; N, 8.07. Found: C, 58.51; H, 3.50; N, 8.16.

By a similar method, the following adducts (**3**) were prepared.

3a: ^{1}H NMR δ ($CDCl_3$) 4.4 (br s, 2 H), 5.93 (s, 1 H), 7.2–7.7 (m, 9 H), and 7.7–8.0 (m, 2 H). **3a** was very unstable and pure compound could not be obtained. It was converted to monoacetyl derivative for identification.

N-Acetyl derivative of **3a**: mp 172–174 °C (hexane–ethyl acetate); IR ν_{max} (KBr) 3250, 1665, 1530 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 2.12 (s, 3 H), 6.83 (s, 1 H), 7.20 (s, 1 H), 7.2–7.6 (m, 8 H), 7.6–7.9 (m, 2 H), 7.98 (s, 1 H).

Anal. Calcd for $C_{19}H_{16}N_2OS$: C, 71.22; H, 5.03; N, 8.74. Found: C, 71.28; H, 5.03; N, 8.68.

3b: mp 165–170 °C (hexane–ether); ^{1}H NMR δ ($CDCl_3$) 2.39 (s, 3 H), 4.32 (br s, 2 H), 5.91, 5.93 (each s, total 1 H), 7.1–7.6 (m, 7 H), 7.84, 7.89 (each a half ABq, *J* = 8.1, 8.8 Hz, total 2 H).

Anal. Calcd for $C_{18}H_{15}N_2SCl$: C, 66.15; H, 4.63; N, 8.57. Found: C, 65.97; H, 4.55; N, 8.52.

3c: IR ν_{max} (KBr) 3500–3300, 1600, 1490, 1420, 1190 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 4.14 (br s, 2 H), 5.84, 5.87 (each s, total 1 H), 6.9–7.7 (m, 7 H), 7.7–8.0 (m, 2 H); mass spectrum, *m/e* 330 (M^+, 10%), 332 (M^+ + 2, 6%), 209 (M^+ − 121, 100%).

3e: mp 151–153 °C (hexane–ether); IR ν_{max} (KBr) 3400 cm^{-1}; ^{1}H NMR δ (Me_2SO-d_6) 5.73, 5.88 (each s, total 1 H), 5.9–6.3 (br s, 2 H), 7.3–8.2 (m, 7 H).

Anal. Calcd for $C_{17}H_{11}N_2SCl_3$: C, 53.49; H, 2.90; N, 7.34. Found: C, 53.38; H, 2.85; N, 7.23.

3f: mp 50–60 °C; ^{1}H NMR δ ($CDCl_3$) 4.10, 4.20 (each br s, total 2 H), 5.60, 6.10 (each s, total 1 H) 6.92, 7.67 (each s, total 1 H), 7.2–7.6 (m, 3 H), 7.7–8.0 (m, 4 H); mass spectrum, *m/e* 380 (M^+, 100%), 382 (M^+ + 2, 103%), 384 (M^+ + 4, 36%).

The ratio between the α and β form was evaluated from each integral value of the vinyl proton in ^{1}H NMR spectrum.

3-Phenyl-5-phenacylisothiazole (10a). Exposure of crude **3a** (220 mg, 0.8 mmol) on silica gel afforded 32 mg (18%) of **10a** as a colorless solid: mp 131–133 °C; IR ν_{max} (KBr) 3300, 3130, 1600, 1570, 1530 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 4.68 (s, 2 H), 7.2–7.6 (m, 7 H), 7.6–8.2 (m, 4 H); mass spectrum, *m/e* 279 (M^+).

Anal. Calcd for $C_{17}H_{13}NOS$: C, 73.09; H, 4.69; N, 5.01. Found: C, 72.81; H, 4.51; N, 4.92.

3-(*p*-Chlorophenyl)-5-(*p*-chlorophenacyl)isothiazole (10b). **3c** (100 mg, 0.29 mmol) was heated under reflux for 2.5 h with oxalic acid (30

(32) Doyle, F. P.; Hanson, J. C.; Long, A. A. W.; Nayler, J. H. C.; Stove, E. R. *J. Chem. Soc.* **1963**, 5838.

mg) in ethanol (40 mL) containing 4 mL of water. After usual workup, 0.1 g of a solid was obtained. Thin-layer chromatographic separation gave 70 mg (70%) of **10b**: mp 206–209 °C; ^{1}H NMR δ ($CDCl_3$) 4.77 (s, 2 H), 7.2–8.2 (m, 9 H); mass spectrum, *m/e* 347 (M^+), 348 (M^+ + 1), 349 (M^+ + 2).

^{15}N-Labeled *p*-Chlorobenzonitrile. A mixture of ^{15}N-labeled *p*-chlorobenzamide (0.90 g, 5.8 mmol), prepared from *p*-chlorobenzoyl chloride and ammonia (^{15}N, 99%), and phosphorus pentoxide (2 g, 14 mmol) was slowly heated with a free flame for 10 min to sublime a colorless solid. The resulting mixture was triturated with ether and the combined organic solution was concentrated to yield a crude product. Sublimation and recrystallization from hexane gave 0.47 g (59%) of ^{15}N-Labeled *p*-chlorobenzonitrile: mp 91–93 °C; mass spectrum, *m/e* 138 (M^+, 100%), 140 (M^+ + 2, 65%), 103 (M^+ − 35, 64%); ^{15}N NMR δ ($CDCl_3$) 257.7 ppm (s).[14a]

^{15}N-Labeled 3-(*p*-chlorophenyl)-5-[2-amino-2-(*p*-chlorophenyl)-vinyl]isothiazole (**3d***) was prepared as before. Recrystallization from hexane–ether afforded a pure sample (57%): mp 138–141 °C; ^{1}H NMR δ ($CDCl_3$) 4.31 (d, $^{1}J_{^{15}NH}$ = 87.0 Hz, 2 H/2), 4.0–4.6 (br s, 2 H/2), 5.88 (d, $^{3}J_{^{15}NH}$ = 4.2 Hz, 1 H/2), 5.88 (s, 1 H/2), 7.38, 7.86 (ABq, J = 8.6 Hz, 8 H/2), 7.33 (d, $^{3}J_{^{15}NH}$ = 3.5 Hz, 1 H/2), 7.33 (s, 1 H/2), 7.38, 7.48 (ABq, J = 9.0 Hz, 8 H/2); ^{13}C NMR δ ($CDCl_3$) 92.5 (d), 116.98 (d), 127.35 (d), 128.02 (d), 128.78 (d), 128.87 (d), 133.23 (d and s), 134.88 (s), 135.15 (s), 136.95 (s), 145.49 (d and s), 164.45 (s), 165.79 (s); ^{15}N NMR δ ($CDCl_3$)[14a] 68.7 (d t, $^{1}J_{^{15}NH}$ = 88.9, $^{3}J_{^{15}NH}$ = 4.3 Hz), 267.6 (s); mass spectrum, *m/e* 347 (M^+, 33%), 349 (M^+ + 2, 23%), 209 (100%). The mass spectrum of **3d*** indicated that the level of enrichment was more than 97%. In the proton-decoupled ^{13}C NMR spectrum, the ^{15}N-substituted carbons appeared at δ 133.23 (d, $^{1}J_{^{15}N^{13}C}$ = 6.9 Hz) and 145.49 (d, $^{1}J_{^{15}N^{13}C}$ = 11.7 Hz).

3-(*p*-Chlorophenyl)-5-[(trimethylsilyl)methyl]isothiazole (12a). To a cold solution (−78 °C) of lithium diisopropylamide, prepared from *n*-butyllithium (3.2 mL of 1.6 M hexane solution) and diisopropylamine (0.74 mL, 5.2 mmol) in 40 mL of dry THF, was added a solution of **4b** (1.00 g, 4.8 mmol) in the same solvent (10 mL). After 30 min of stirring, trimethylsilyl chloride (0.66 mL, 5.2 mmol) was added to the reaction mixture at −78 °C. After it was stirred at −78 °C for 2 h, the mixture was poured onto ice–water and extracted with ether. Workup in the usual manner gave 1.31 g of a crystalline product. Recrystallization from hexane afforded 1.12 g (83%) of **12a** as a colorless solid: mp 72–73 °C; IR ν_{max} (KBr) 3100–2700, 1490, 1420, 1250 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 0.09 (s, 9 H), 2.43 (s, 2 H), 7.07 (s, 1 H), 7.33, 7.80 (ABq, J = 8 Hz, 4 H); mass spectrum, *m/e* 281 (M^+, 100%), 282 (M^+ + 1, 20%), and 283 (M^+ + 2, 44%).

Anal. Calcd for $C_{13}H_{16}NSClSi$: C, 55.39; H, 5.72; N, 4.97. Found: C, 55.50; H, 5.81; N, 4.92.

3-(*p*-Chlorophenyl)-5-[(*tert*-butyldimethylsilyl)methyl]isothiazole (12b). By means of the above procedure, **4b** (3.85 g, 18.4 mmol) was silylated with *tert*-butyldimethylsilyl chloride in 98% yield to give **12b** (5.85 g). Recrystallization from hexane gave a pure sample as colorless crystals: mp 81–83 °C; IR ν_{max} (KBr) 1490, 1085, 800 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 0.05 (s, 6 H), 0.93 (s, 9 H), 2.43 (s, 2 H), 7.12 (s, 1 H), 7.36, 7.83 (ABq, J = 8 Hz, 4 H).

Anal. Calcd for $C_{16}H_{22}NSClSi$: C, 59.32; H, 6.84; N, 4.32. Found: C, 59.61; H, 6.77; N, 4.54.

1,3-Silyl Group Rearrangement. 3-(*p*-Chlorophenyl)-5-[2-[(*tert*-butyldimethylsilyl)amino]-2-(*p*-chlorophenyl)vinyl]isothiazole (13d-*Z*). A solution of **12b** (0.50 g, 1.5 mmol) in dry THF (6 mL) was treated at −78 °C for 3 h with lithium diisopropylamide prepared from *n*-butyllithium (1.16 mL) and diisopropylamine (0.26 mL) in THF (6 mL) followed by addition of *p*-chlorobenzonitrile (0.28 g, 1.8 mmol) at the same temperature. The reaction mixture was stirred at 0 °C for 15 h. After the usual workup, recrystallization from ether–hexane gave a pure sample (**13d-*Z***, 0.42 g, 61%) as colorless crystals: mp 128–130 °C; IR ν_{max} (KBr) 2950–2800, 2300, 2050, 1590, 1490, 1400 cm^{-1}; UV λ_{max} (log ϵ, MeOH) 255 (4.38), 275 (4.39), 348 nm (4.36); ^{1}H NMR δ ($CDCl_3$) −0.05 (s, 6 H), 1.04 (s, 9 H), 3.78 (br s, 1 H), 5.86 (s, 1 H), 7.32 (s, 1 H), 7.41, 7.87 (ABq, J = 8 Hz, 4 H), 7.38 (s, 4 H); mass spectrum, *m/e* 460 (M^+, 41%), 461 (M^+ + 1, 14%), 462 (M^+ + 2, 28%), 403 (M^+ − 57, 100%).

Anal. Calcd for $C_{23}H_{26}N_2SCl_2Si$: C, 59.86; H, 5.68; N, 6.07. Found: C, 59.74; H, 5.68; N, 5.99.

When the pure **13d-*Z*** in $CDCl_3$ solution was allowed to stand at room temperature for 3 days, isomerization occurred to result in a 1:1 mixture of **13d-*Z*** and the geometric isomer **13d-*E***.

On the other hand, reaction of **12a** with *p*-chlorobenzonitrile under the same conditions gave rise to the desilylated product **3d** in moderate yield.

^{15}N-Labeled 3-(*p*-Chlorophenyl)-5-[2-[(*tert*-butyldimethylsilyl)-amino]-2-(*p*-chlorophenyl)vinyl]isothiazole (13d*-*Z*). By means of the procedure described for **13d-*Z***, ^{15}N-labeled **13d-*Z*** (86 mg, 30%) was obtained from 200 mg (0.62 mmol) of **12b** in THF (3 mL), ^{15}N-labeled *p*-chlorobenzonitrile (200 mg, 0.62 mmol), and *n*-butyllithium (0.51 mL of 1.47 M hexane solution) as a base without using LDA.

13d*-*Z*: ^{1}H NMR δ ($CDCl_3$) −0.07 (d, $^{3}J_{^{15}NH}$ = 0.9 Hz, 6 H), 1.00 (s, 9 H), 3.81 (d, $^{1}J_{^{15}NH}$ = 72.3 Hz, 1 H), 5.83 (d, $^{3}J_{^{15}NH}$ = 3.5 Hz, 1 H), 7.33 (s, 1 H), 7.37, 7.40 (ABq, J = 9.0 Hz, 4 H), 7.40, 7.88 (ABq, J = 8.8 Hz, 4 H).

3-(*p*-Chlorophenyl)-5-[2-[(*tert*-butyldimethylsilyl)amino]-2-*p*-tolylvinyl]isothiazole (13b). By means of the procedure for **13d-*Z***, treatment of **12b** (1.00 g, 3.1 mmol) in THF (5 mL) with *n*-butyllithium (3.2 mL of 1.6 M hexane solution) and *p*-toluonitrile (0.54 g, 4.6 mmol in 2 mL of THF) gave **13b-*Z*** (0.62 g, 45%) as colorless crystals: mp 114–116 °C; ^{1}H NMR δ ($CDCl_3$) −0.08 (s, 6 H), 1.12 (s, 9 H), 2.38 (s, 3 H), 3.75–3.90 (br s, 1 H), 5.82 (s, 1 H), 7.30 (s, 1 H), 7.17, 7.35 (ABq, J = 8.6 Hz, 2 H), and 7.41, 7.86 (ABq, J = 8.7 Hz, 2 H); mass spectrum, *m/e* 440 (M^+), 442 (M^+ + 2, 23%), and 383 (M^+ − 57, 100%).

Anal. Calcd for $C_{24}H_{29}N_2SSiCl$: C, 65.35; H, 6.63; N, 6.35. Found: C, 65.60; H, 6.70; N, 6.22.

3-(*p*-Chlorophenyl)-5-[2-[(*tert*-butyldimethylsilyl)amino]-2-(3,5-dichlorophenyl)vinyl]isothiazole (13e). By means of the procedure for **13d-*Z***, treatment of **12b** (0.50 g, 1.54 mmol) with 1.6 mL of *n*-butyllithium (1.6 M hexane solution) followed by addition of 3,5-dichlorobenzonitrile (0.40 g, 2.31 mmol) in 5 mL of THF afforded 450 mg (58%) of **13e** after recrystallization from ether–pentane: mp 170–173 °C; IR ν_{max} (KBr) 1590, 1419, and 1080 cm^{-1}; UV λ_{max} (log ϵ, MeOH) 255 (4.39), 347.5 nm (4.30); ^{1}H NMR δ ($CDCl_3$) −0.01 (s, 6 H), 1.00 (s, 9 H), 3.7 (br s, 1 H), 5.90 (s, 1 H), 7.38 (s, 4 H), 7.42, 7.87 (ABq, J = 9 Hz, 4 H); mass spectrum, *m/e* 495 (M^+), 496 (M^+ + 2).

Anal. Calcd for $C_{23}H_{25}N_2Cl_3SSi$: C, 55.70; H, 5.08; N, 5.65. Found: C, 55.59; H, 4.95; N, 5.50.

Preparation of Pure α Form of 3 by Desilylation of 13. 3-(*p*-Chlorophenyl)-5-(2-amino-2-*p*-tolylvinyl)isothiazole (3b-α). A cold solution of **13b** (140 mg, 0.317 mmol) in dry THF (2.5 mL) was treated with tetra-*n*-butylammonium fluoride (0.64 mL of 1 M THF solution) at −78 °C for 2 h. The mixture was diluted with water at −78 °C and extracted with ether. The organic layer was washed with water, dried over potassium carbonate, and evaporated. Recrystallization of the residue from ether–hexane afforded 59.6 mg (57%) of **3b-α** as a pure sample: mp 168–170 °C; ^{1}H NMR δ ($CDCl_3$) 2.39 (s, 3 H), 4.32 (br s, 2 H), 5.93 (s, 1 H), 7.42 (s, 1 H), 7.30, 7.47 (ABq, J = 8.4 Hz, 4 H), 7.41, 7.89 (ABq, J = 8.8 Hz, 4 H); ^{1}H NMR δ (C_6D_6) 2.11 (s, 3 H), 3.3–3.8 (br s, 2 H), 5.83 (s, 1 H), 6.9–7.3 (overlapped with protons contained in benzene-d_6), 7.82 (ABq, J = 8.8 Hz, 2 H).

Anal. Calcd for $C_{18}H_{15}N_2SCl$: C, 66.15; H, 4.63; N, 8.57. Found: C, 65.97; H, 4.55; N, 8.52.

^{15}N-Labeled 3-(*p*-Chlorophenyl)-5-[2-amino-2-(*p*-chlorophenyl)-vinyl]isothiazole (3d*-α-*Z*). Tetrabutylammonium fluoride (0.37 mL of 1 M THF solution) was added to a stirred solution of **13d*-*Z*** (86.0 mg, 0.186 mmol) in THF (3 mL) at −78 °C under a nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 0.5 h. Workup in the predescribed manner gave 30.4 mg of **3d*-α-*Z*** (47%) as a yellow solid: ^{1}H NMR δ ($CDCl_3$) 4.31 (d, $^{1}J_{^{15}NH}$ = 87.0 Hz, 2 H), 5.88 (d, $^{3}J_{^{15}NH}$ = 4.2 Hz, 1 H), 7.38, 7.86 (ABq, J = 8.6 Hz, 4 H), 7.33 (s, 1 H), 7.38, 7.48 (ABq, J = 9.0 Hz, 4 H); ^{1}H NMR δ (benzene-d_6) 3.48 (d, $^{1}J_{^{15}NH}$ = 86.5 Hz, 2 H), 5.63 (d, $^{3}J_{^{15}NH}$ = 4.0 Hz, 1 H), 7.0–7.2 (overlapped with protons contained in benzene-d_6), 7.19–7.81 (ABq, J = 9.0 Hz, 4 H) (see Figure 1b).

3-(*p*-Chlorophenyl)-5-[2-amino-2-(3,5-dichlorophenyl)vinyl]isothiazole (3e-α). By the similar procedure described above, **3e-α** was obtained in 70% yield from 97.1 mg (0.196 mmol) of **13e**. Recrystallization from ether–hexane gave a pure **3e-α**: mp 168–174 °C; ^{1}H NMR δ (Me_2SO-d_6) 5.87 (s, 1 H), 6.02 (br s, 2 H), 7.48, 8.06 (ABq, J = 8 Hz, 4 H), 7.58 (t, J = 1 Hz, 1 H), 7.63 (d, J = 1 Hz, 2 H), 7.84 (s, 1 H); ^{1}H NMR δ (C_6D_6) 5.44 (s, 1 H), 6.96 (s, 1 H), 7.05–7.25 (overlapped with protons contained in benzene-d_6), 7.18, 7.82 (ABq, J = 8.8 Hz, 4 H).

Anal. Calcd for $C_{17}H_{11}N_2SCl_3$: C, 53.49; H, 3.09; N, 7.34. Found: C, 53.41; H, 3.06; N, 7.14.

Photoisomerization of 13d-*Z* into 13d-*E*. A sample of **13d-*Z*** (30 mg, 0.065 mmol) in ether (20 mL) was irradiated through a Pyrex filter by a high-pressure mercury lamp (Eiko-shya Co. PIH-100) for 4 h under nitrogen atmosphere. After evaporation of the solvent, fractional recrystallization of the residue from pentane gave 13 mg of **13d-*E*** of ca. 90% purity: mp 123–124 °C; UV λ_{max} (log ϵ, MeOH) 276 (4.52), 350 nm (4.23); ^{1}H NMR δ ($CDCl_3$) 0.27 (s, 6 H), 0.98 (s, 9 H), 3.35 (br s, 1 H), 6.00 (s, 1 H), 6.91 (s, 1 H), 7.40 (s, 4 H), 7.33, 7.73 (ABq, J = 9 Hz, 4 H); mass spectrum, *m/e* 460 (M^+, 100%), 461 (M^+ + 1, 26%), 462 (M^+ + 2, 76%), 403 (M^+ − 57).

Anal. Calcd for $C_{23}H_{26}N_2SCl_2Si$: C, 59.86; H, 5.68; N, 6.07. Found: C, 59.84; H, 5.82; N, 6.01.

(*E*)-3-(*p*-Chlorophenyl)-5-[2-(*p*-chlorophenyl)vinyl]isothiazole (14-*E*). To a solution of 3-(*p*-chlorophenyl)-5-methylisothiazole (**4b**, 0.5 g, 2.4 mmol) and potassium *tert*-butoxide (0.32 g, 2.9 mmol) in dry THF (20 mL) was added *p*-chlorobenzaldehyde (0.4 g, 2.9 mmol) at room temperature. The reaction mixture was stirred for 2 days. After usual workup, chromatography of the residue on silica gel gave 0.30 g (38%) of **14**-*E* as colorless solid: mp 157–158 °C; ^{1}H NMR δ ($CDCl_3$) 7.12, 7.16 (ABq, *J* = 16 Hz, 2 H), 7.33, 7.41 (ABq, *J* = 9 Hz, 4 H), 7.50 (s, 1 H), and 7.43, 7.88 (ABq, *J* = 8.8 Hz, 4 H); ^{1}H NMR δ ($CDCl_3$ + CF_3CO_2H) 7.21 (s, 2 H), 7.37, 7.49 (ABq, *J* = 9 Hz, 4 H), 7.49 (s, 1 H), and 7.48, 7.77 (ABq, *J* = 8.8 Hz, 4 H); UV λ_{max} (log ε, MeOH) 230 (4.09), 270 (4.31), 320 nm (4.43).

Anal. Calcd for $C_{17}H_{11}NSCl_2$: C, 61.46; H, 3.34; N, 4.22. Found: C, 61.41; H, 3.35; N, 4.23.

(*Z*)-3-(*p*-Chlorophenyl)-5-[2-(*p*-chlorophenyl)vinyl]isothiazole (14-*Z*). By the method as described above, photoisomerization of **14**-*E* (55 mg, 0.17 mmol) resulted in a mixture of **14**-*E* and **14**-*Z*. Thin-layer chromatographic separation of the mixture gave **14**-*Z* (32 mg) along with **14**-*E* (22 mg).

14-*Z*: mp 133.5–134 °C; ^{1}H NMR δ ($CDCl_3$) 6.80 (s, 2 H), 7.30 (s, 1 H), 7.28, 7.42 (ABq, *J* = 9 Hz, 4 H), 7.39, 7.78 (ABq, *J* = 8.8 Hz, 4 H); ^{1}H NMR δ ($CDCl_3$ + CF_3CO_2H) 6.94, 7.34 (ABq, *J* = 11.7 Hz, 2 H), 7.24, 7.53 (ABq, *J* = 8.2 Hz, 4 H), 7.45 (s, 1 H), 7.52, 7.71 (ABq, *J* = 9 Hz, 4 H); UV λ_{max} (log ε, MeOH) 257 (4.43), 280 (4.32, shoulder), and 300 nm (4.20, shoulder).

Anal. Calcd for $C_{17}H_{11}NSCl_2$: C, 61.46; H, 3.34; N, 4.22. Found: C, 61.44; H, 3.28; N, 4.24.

Bond Switching Equilibration of 3. A solution of **3b**-α (5 mg, 0.015 mmol) in benzene-d_6 (0.4 mL) was allowed to stand at 42 °C for 1 day to result in equilibrium between **3b**-α and **3b**-β, the ratio being 58:42 evaluated from the integral value of each vinyl proton in the ^{1}H NMR spectrum. Since the mixture consisted of only two components and the spectrum of **3b**-α had been recorded, it was an easy matter to assign ^{1}H NMR signals for **3b**-β by subtraction of those of **3b**-α.

Such a bond switch was also observed for **3e** and **3d***. Therefore, by the same methodology, spectral data of **3e**-β and **3d***-β were also easily estimated. The spectra of **3b,d*,e** obtained by the ring transformation equilibrium were superimposable upon those of the sample prepared by direct coupling reaction of **4** with the corresponding benzonitrile.

3b-β: ^{1}H NMR δ ($CDCl_3$) 2.39 (s, 3 H), 4.32 (br s, 2 H), 5.91 (s, 1 H), 7.1–7.6 (m, 7 H), 7.84 (half ABq, *J* = 8.1 Hz, 2 H); ^{1}H NMR δ (C_6D_6) 2.11 (s, 3 H), 3.3–3.8 (br s, 2 H), 5.65 (s, 1 H), 6.9–7.3 (overlapped with protons contained in benzene-d_6), 8.06 (half ABq, *J* = 8.1 Hz, 2 H).

3e-β: ^{1}H NMR δ (Me_2SO-d_6) 5.74 (s, 1 H), 5.8–6.1 (br s, 2 H), 7.46, 7.68 (ABq, *J* = 9.0 Hz, 4 H), 7.53 (t, *J* = 2.0 Hz, 1 H), 7.91 (s, 1 H), 8.07 (d, *J* = 2.0 Hz, 2 H); ^{1}H NMR δ (C_6D_6) 3.1–3.5 (br s, 2 H), 5.58 (s, 1 H), 6.81 (s, 1 H), 7.05–7.25 (overlapped with protons contained in benzene-d_6), 7.87 (d, *J* = 2.0 Hz, 2 H).

3d*-α-*Z*: ^{1}H NMR δ (benzene-d_6) 3.2–3.7 (br s, 2 H), 5.62 (s, 1 H), 7.0–7.2 (overlapped with protons contained in benzene-d_6), 7.19, 7.81 (ABq, *J* = 9.0 Hz, 4 H); ^{1}H NMR δ ($CDCl_3$) 4.0–4.6 (br s, 2 H), 5.88 (s, 1 H), 7.33 (d, $^3J_{^{15}NH}$ = 3.5 Hz, 1 H), 7.38, 7.86 (ABq, *J* = 8.6 Hz, 4 H), 7.38, 7.48 (ABq, *J* = 9.0 Hz, 4 H).

Kinetic Studies. The Hitachi R-90H FT NMR instrument was used for all measurements. For each run, approximately 5 mg of **3**-α was dissolved into 0.4 mL of deuterated solvent (Me_2SO-d_6 or benzene-d_6) in a 5-mm NMR tube which was placed at the instrument probe. At appropriate intervals, the integral ratios of vinyl proton for **3b,e**-α and **3b,e**-β were monitored. In the case of **3d***, the characteristic signals of amino protons ($^{14}NH_2$ and $^{15}NH_2$) were used to monitor the reaction. The reversible first-order rate constants, k_1, were calculated from the slope of the linear plots of ln $(m/(m - x))$ vs. time (t) by using the least-squares method. The parameter *m* equals the mole fraction of β form at the equilibrium and *x* means the mole fraction of **3**-β at an appropriate time (t).[22]

Determination of Molecular Weight of 3b,d,e. The molecular weight of **3b,d,e** was determined by vapor pressure osmometry (Knauer Co.) in the range 0.005–0.020 M in benzene solution: **3b**, 340 (calcd, 327); **3d**, 343 (347); **3e**, 390 (382).

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Registry No. 3a-*Z*, 95514-26-4; **3a**-*Z* (*N*-acetyl derivative), 95514-27-5; **3b**-α-*Z*, 95514-28-6; **3b**-β-*Z*, 95514-29-7; **3c**-α-*Z*, 95514-30-0; **3c**-β-*Z*, 95514-31-1; **3d**-*Z*, 95514-25-3; **3d***-α-*Z*, 95514-38-8; **3d***-β-*Z*, 95514-44-6; **3e**-α-*Z*, 95514-32-2; **3e**-β-*Z*, 95514-33-3; **3f**-α-*Z*, 95514-34-4; **3f**-β-*Z*, 95514-35-5; **4a**, 13369-71-6; **4b**, 94225-34-0; **5**, 3848-36-0; **6**, 68870-58-6; **7**, 91182-87-5; **8**, 95514-22-0; **9a**, 95514-24-2; **9b**, 95514-23-1; **10a**, 95514-36-6; **10b**, 95514-37-7; **12a**, 95514-39-9; **12b**, 94225-36-2; **13b**-*Z*, 95514-42-4; **13d**-*Z*, 95514-40-2; **13d**-*E*, 95514-47-9; **13d***-*Z*, 95514-41-3; **13e**-*Z*, 95514-43-5; **14**-*E*, 95514-45-7; **14**-*Z*, 95514-46-8; *p*-ClC_6H_4CN, 623-03-0; $MeCOCH_2CO_2Me$, 105-45-3; *p*-$ClC_6H_4C^{15}N$, 36093-33-1; *p*-$ClC_6H_4CO^{15}NH_2$, 31656-61-8; 3-phenyl-5-methylisoxazole, 1008-74-8.

Acyclic Diastereoselection as a Synthetic Route to Quassinoids: A Claisen Rearrangement Based Strategy for Bruceantin

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Abstract: A highly stereoselective Claisen rearrangement of allyl vinyl ether **17** gives rise to β-keto ester **18** having the correct relative stereochemistry at C_8, C_9, and C_{14} of the quassinoids. Efficient, rapid assembly of rings C, D, and E is achieved. The model sets the stage for an eventual synthesis of (−)-bruceantin from keto acid **9b**.

Bruceantin (**1**) is a physiologically active quassinoid isolated from *Brucea antidysenterica Mill.*, a Simaroubaceous tree indigenous to Ethiopia, which has been utilized in the treatment of cancer.[1] The initial activity of bruceantin toward a number of cancer screens sparked interest in this substance at the National Cancer Institute (NSC 165563) and rekindled the synthetic chemists' interest in the area of quassinoids,[2] a field marked heretofore by the contributions of Dias[3] and Valenta.[4]

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