CHLORINATION OF 5-[2-(*N*-SILYLAMINO)VINYL]-ISOTHIAZOLE AND RELATED DERIVATIVES WITH *N*-CHLOROSUCCINIMIDE. INHIBITION OF RING-TRANSFORMATION (BOND SWITCH) BY STERIC HINDRANCE

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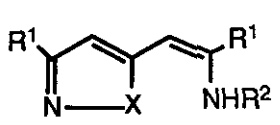
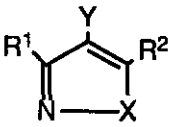
Abstract- The selective monochlorination of 5-[2-(*N*-silylamino)vinyl]isothiazoles (**1a,b**) and their related compounds (**1c,d**, **2a-g**, **3a-c**, and **4a,b**) with *N*-chlorosuccinimide is described. Chlorination of **1a,b** occurred at vinyl carbon to give **5a,b** and the geometry was determined to be *Z*-isomer according to spectral data. It is noteworthy that **1d** smoothly occurred bond switch at room temperature but **5d** did not ring-transform under the same conditions.

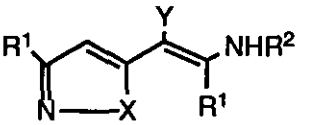
There are several investigations on chlorination with *N*-chlorosuccinimide (NCS) of electron rich aromatic ring including heteroaromatic ring.[1] In previous papers,[2,3] we reported various interesting phenomena (bond switching and restricted rotation) in 10-S-3 sulfurane and related systems. In this paper, we describe the results of investigation on chlorination of 5-(2-aminovinyl)isoazole derivatives (**1a-d**) and isoazole derivatives (**2a** and **4a,b**).



	R^1	R^2	X
1a	*p*-ClC_6H_4	t-$BuMe_2Si$	S
1b	C_6H_5	t-$BuMe_2Si$	S
1c	C_6H_5	t-$BuMe_2Si$	O
1d	*p*-ClC_6H_4	H	S



	R^1	R^2	X	Y
2a	*p*-ClC_6H_4	Me	S	H
2b	C_6H_5	Me	S	H
2c	C_6H_5	Me	O	H
3a	C_6H_5	t-$BuMe_2SiCH_2$	S	H
3b	C_6H_5	t-$BuMe_2SiCH_2$	S	H
3c	C_6H_5	t-$BuMe_2SiCH_2$	O	H
4a	Me	NH_2	S	H
4b	Me	t-$BuMe_2SiNH$	S	H
7a	*p*-ClC_6H_4	Me	S	Cl
7b	Me	NH_2	S	Cl
7c	Me	t-$BuMe_2SiNH$	S	Cl

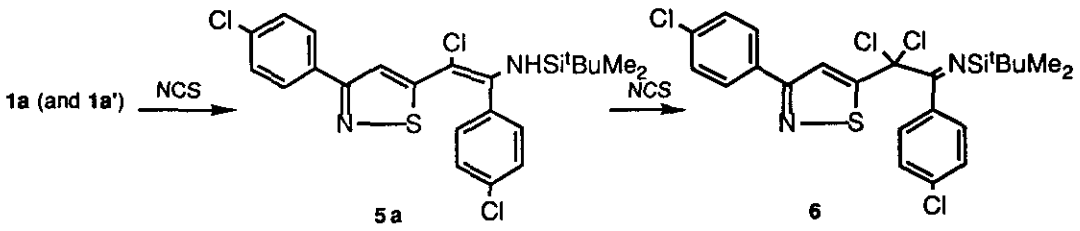


	R^1	R^2	X	Y
1a'	*p*-ClC_6H_4	t-$BuMe_2Si$	S	H
5a	*p*-ClC_6H_4	t-$BuMe_2Si$	S	Cl
5b	C_6H_5	t-$BuMe_2Si$	S	Cl
5c	C_6H_5	t-$BuMe_2Si$	O	Cl
5d	*p*-ClC_6H_4	H	S	Cl

RESULTS AND DISCUSSION

Each substrate for chlorination was prepared by the modified method reported previously.[2,3c] Silylation of isoazole derivatives (**2a-c** and **4a**) gave **3a-c** and **4b** under basic conditions. Aminovinylisoazoles (**1a-d**) were prepared by reaction of isoazole (**2a** and **3a-c**) with the corresponding nitrile.[2] Treatment of **1a** with excess sodium chlorite in aqueous methanol at 25 °C for 20 h resulted in a mixture of mono and dichloro derivative depending upon the reaction conditions. In contrast, however, exposure of the geometric pure sample (**1a**) or the geometric mixture of **1a** and **1a'** to 1 equiv. of NCS in methylene chloride solution at 25 °C immediately resulted in formation of a monochlorinated derivative (**5a**) in 88% yield. On the basis of ^1H nmr spectrum and thin-layer chromatographic analysis the chloride (**5a**) consisted of a single isomer. In the ^1H nmr spectrum in $CDCl_3$ solution, there were observed the following characteristic signals, δ 7.15 (s, 1H), 7.33 and 7.55 (ABq, J = 8 Hz, 4H), 7.37 and 7.77 (ABq, J = 9 Hz, 4H), and 5.02 (br s, 1H) together with signals for silylmethyl and *tert*-butyl group. The vinyl proton signal at δ 5.83 in the starting material (**1a**) disappeared in the ^1H nmr spectrum of the product but the uv spectrum of **5a** was similar to that of **1a'** rather than **1a** as shown in Figure 1 A and B. The spectral evidences were in agreement with the assigned *Z*-geometry for **5a**. The *Z*-geometry must be thermodynamically more stable than the *E*-geometry.

Furthermore, treatment of **1a** with 2 equiv. of NCS afforded a dichlorinated derivative (**6**) in 91% yield without removal of the silyl group. The structural assignment was founded upon spectral data and elemental analysis. The heterocyclic proton appeared as a singlet at δ 7.98 along with the other signals in $CDCl_3$ solution. The uv spectrum (Figure 1 C) of **6** was very different from that of **1a** or **1a'**. According to the spectral data, the structure of **6** was assigned to geminal dichloro derivative in which the isothiazole ring is not conjugated with another benzene ring.



Scheme 1

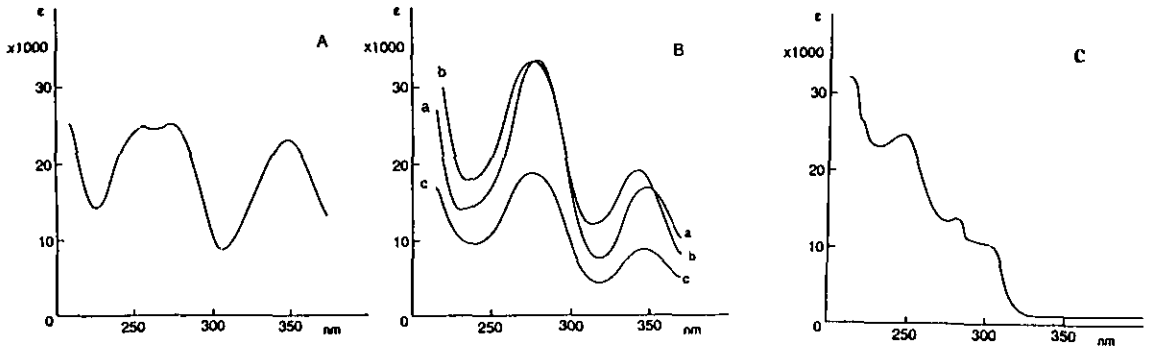
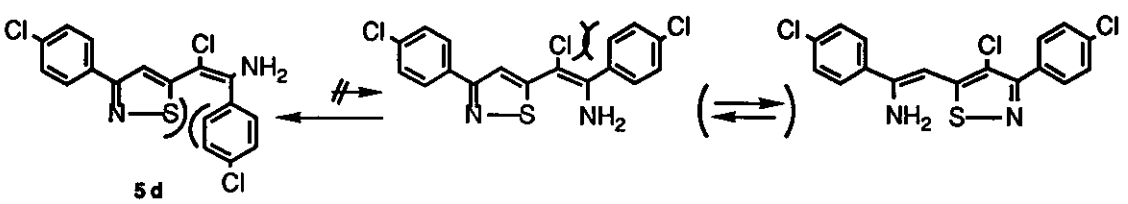


Figure 1. (A): uv spectrum of **1a** in methanol. (B): uv spectra of **1a'** (a), **5a** (b), and **5d** (c) in methanol. (C): uv spectrum of **6** in methanol.

Under the same conditions, the other related monochloro derivatives (**5b-d**) were obtained in high yields. Treatment of **5a** with tetrabutylammonium fluoride furnished desilylated product (**5d**) in high yield. Furthermore, reaction of isothiazole derivatives (**2a** and **4a,b**) with NCS gave **7a-c** respectively.

It is interesting from the view point of bond switch that the geometric isomerization did not occur in the monochloro substrate (**5a-d**), while there had been observed the equilibrium between geometric isomers in the starting materials (**1a** and **1a'**).[2] The results indicate that steric repulsion[4] between the benzene ring and the chloro group would be much larger as compared with that between the benzene and the isothiazole rings. Furthermore, it is noteworthy that there was no observation of the ring-transformation in **5d** after several days at 50 °C.[2,5] Therefore, it is considered that N-S·····N linear arrangement in 5-aminovinylisothiazole system such as **1d** must be one of the important factors for the bond switching.[2,3c,5]



Scheme 2

EXPERIMENTAL

All the melting points are uncorrected. The ir spectra were obtained with a Hitachi 215 grating ir spectrophotometer. The ^1H nmr measurements were carried out on a Varian T-60 instrument and Hitachi R-90H, using tetramethylsilane as the internal reference. The uv spectra were measured on a Hitachi-124 spectrophotometer. The spectral data of each compounds (**5b-d**, **6**, and **7a-c**) are summarized in Table I. Isoazole derivatives (**1a**, **1d**, **2a-c**, **3a**, and **4a**) were prepared by the method described previously.[2,3c]

(*Z*)-5-[2-(*tert*-Butyldimethylsilyl)amino-2-phenylvinyl]-3-phenylisothiazole (1b). To a cold solution (-78 °C) of lithium diisopropylamide, prepared from n-butyllithium (2.98 ml of 1.6 M hexane solution, 4.8 mmol) and diisopropylamine (0.67 ml, 4.7 mmol) in 15 ml of dry tetrahydrofuran, was added a solution of **2b** (690 mg, 3.97 mmol) in the same solvent (5 ml). After 30 min of stirring, *tert*-butyldimethylsilyl chloride (720 mg, 4.7 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 and flash-chromatography on silica gel (hexane-ether; 100 : 1) gave a crystalline product. Recrystallization from hexane afforded **3b** (970 mg, 78%): mp 68-69 °C (from hexane); ir (KBr) 1500, 1450, 1370, 1140, and 810 cm^{-1}; ^1H nmr ($CDCl_3$) δ = 0.13 (s, 6H), 1.08 (s, 9H), 2.58 (s, 2H), 7.22 (s, 1H), 7.35-7.58 (m, 3H), and 7.88-8.12 (m, 2H). *Anal.* Calcd for $C_{16}H_{23}NSSi$: C, 66.38; H, 8.01; N, 4.84. Found: C, 66.15; H, 8.02; N; 4.83.

A solution of **3b** (0.30 g, 1.04 mmol) in dry tetrahydrofuran (5 ml) was treated at -78 °C for 3 h with n-butyllithium (0.8 ml of 1.6 M hexane solution, 1.3 mmol) followed by addition of benzonitrile (0.13 ml, 1.25 mmol) at the same temperature. The reaction mixture was stirred at 0 °C for 15 h. After usual work-up, recrystallization from pentane afforded a pure sample (**1b**) (230 mg, 66%): mp 81-83 °C; ir (KBr) 3350, 1590, 1400, and 1260 cm^{-1}; ^1H nmr ($CDCl_3$) δ = -0.05 (s, 6H), 1.02 (s, 9H), 3.97 (br s, 1H), 5.95 (s, 1H), 7.3-7.8 (m, 9H), and 7.95-8.2 (m, 2H); ms (m/z) 392 (M^+, 45%), and 335 (100%).

(*Z*)-5-[2-(*tert*-Butyldimethylsilyl)amino-2-phenylvinyl]-3-phenylisoxazole (1c). By the same procedure described above, 3-phenyl-5-(*tert*-butyldimethylsilyl)methylisoxazole (3c) was obtained from **2c** in 79% yield, followed by coupling reaction with benzonitrile to give **1c** (66%) as colorless crystals. For **3c**: mp 63-65 °C (from hexane); ^1H nmr ($CDCl_3$) δ = 0.27 (s, 6H), 1.12 (s, 9H), 2.42 (s, 2H), 6.25 (s, 2H), 7.25-7.58 (m, 3H), and 7.65-7.92 (m, 2H). *Anal.* Calcd for $C_{16}H_{23}NOSi$: C, 70.28; H, 8.48; N, 5.12. Found: C, 70.07; H, 8.64; N, 5.04. For **1c**: mp 117-119 °C (from pentane); ir (KBr) 3380, 1610, 1380, and 1080 cm^{-1}; uv [λ_{max} (log

ε), MeOH] 240 (4.36) and 333 nm (4.40); ^{1}H nmr ($CDCl_3$) δ = -0.01 (s, 6H), 1.12 (s, 9H), 5.43 (s, 1H), 6.11 (bs, 1H), 6.28 (s, 1H), 7.32-7.82 (m, 8H), and 7.82-8.15 (m, 2H). *Anal.* Calcd for $C_{23}H_{28}N_2OSi$: C, 73.36; H, 7.49; N, 7.44. Found: C, 73.35; H, 7.46; N, 7.42.

5-(*tert*-Butyldimethylsilylamino)-3-methylisothiazole (4b). To a cold solution (-78 °C) of **4a** (500 mg, 4.39 mmol) in tetrahydrofuran (5 ml) was added n-butyllithium (3.37 ml of 1.6 M hexane solution, 5.4 mmol). After 30 min of stirring, a solution of *tert*-butyldimethylsilyl chloride (720 mg, 4.7 mmol) in 10 ml of tetrahydrofuran 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 and tlc on silica gel (hexane-ether) gave a crystalline product. Recrystallization from hexane afforded **4b** (540 mg, 54%): mp 91-92 °C (from hexane); ir (KBr) 3150, 1518, and 1390 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ = 0.27 (s, 6H), 0.97 (s, 9H), 2.32 (s, 3H), 4.00-4.40 (br s, 1H), and 6.12 (s, 1H). *Anal.* Calcd for $C_{10}H_{20}N_2SSi$: C, 52.58; H, 8.83; N, 12.26. Found: C, 52.59; H, 9.10; N, 12.24.

(Z)-5-[1-Chloro-2-(*tert*-butyldimethylsilyl)amino-2-*p*-chlorophenylvinyl]-3-*p*-chlorophenylisothiazole (5a). A solution of 98.4 mg (0.213 mmol) of (Z)-3-*p*-chlorophenyl-5-[2-(*tert*-butyldimethylsilyl)amino-2-*p*-chlorophenylvinyl]isothiazole (**1a**)[2] in 5 ml of dichloromethane was treated with 28.9 mg (0.211 mmol) of *N*-chlorosuccinimide at room temperature for 5 min. The reaction mixture was poured into a mixture of ether and water. The organic phase was washed with water prior to drying and solvent evaporation. The crude product was purified by tlc on silica gel (elution with dichloromethane-hexane, 1 : 1) and recrystallization from ether-hexane to afford 93 mg (88%) of a pure sample (**5a**): mp 167.5-168.5 °C; ir (KBr) 3350, 2900, 2050, 1560, 1340, and 1090 cm^{-1}. *Anal.* Calcd for $C_{23}H_{25}N_2Cl_3SSi$: C, 55.70; H, 5.08; N, 5.65; Cl, 21.44. Found: C, 55.42; H, 5.04; N, 5.78; Cl, 21.72.

(Z)-5-[1-Chloro-2-(*tert*-butyldimethylsilyl)amino-2-phenylvinyl]-3-phenylisothiazole (5b), (Z)-5-[1-Chloro-2-(*tert*-butyldimethylsilyl)-

amino-2-phenylvinyl]-3-phenylisoxazole (5c), and (*Z*)-5-(1-Chloro-2-amino-2-*p*-chlorophenylvinyl)-3-*p*-chlorophenylisothiazole (5d). By means of the above procedure, monochlorides (**5b-d**) were obtained in high yields. **5b** and **5c** were not crystallized but the spectral data (Table 1) indicate the assigned structure, respectively. Crystallization and recrystallization of **5d** from hexane-ether furnished a pure sample: mp 132-133.5 °C. *Anal.* Calcd for $C_{17}H_{11}N_2Cl_3S$: C, 53.49; H, 2.90; N, 7.34. Found: C, 53.32; H, 2.80; N, 7.31.

Desilylation of 5a. A mixture of **5a** (34 mg, 0.068 mmol) in 5 ml of tetrahydrofuran was treated with tetra-n-butylammmonium fluoride (0.1 ml of 10% tetrahydrofuran solution) at -78 °C for 2 h. A usual work-up gave 25 mg (96%) of a colorless solid whose spectrum was superimposable upon that of authentic sample (**5d**).

5-[1,1-Dichloro-2-(*tert*-butyldimethylsilyl)imino-2-*p*-chlorophenylethyl]-3-*p*-chlorophenylisothiazole (6). A mixture of **1a** (21.5 mg, 0.0465 mmol) and *N*-chlorosuccinimide (14.0 mg, 0.105 mmol) in 0.3 ml of $CHCl_3$ was allowed to react at room temperature for 1 day. The reaction mixture was poured into a mixture of ether and water. The organic phase was dried and evaporated to leave 22.6 mg (91%) of **6** as a colorless solid: mp 138-139 °C (from ether); ir (KBr) 2950, 1690, 1590, 1400, 1160, and 1080 cm^{-1}. *Anal.* Calcd for $C_{23}H_{24}N_2Cl_4SSi$: C, 52,08; H, 4.56; N, 5.28; Cl, 26.74. Found: C, 51.82; H, 4.51; N, 5.25, Cl, 26.74.

5-[(*tert*-Butyldimethylsilyl)amino]-4-chloro-3-methylisothiazole (7c). A mixture of 3-methyl-5-[(*tert*-butyldimethylsilyl)amino]isothiazole (**4b**)[2] (30 mg, 0.13 mmol) and *N*-chlorosuccinimide (17.5 mg, 0.13 mmol) in 0.5 ml of $CHCl_3$ was allowed at room temperature for 1 h. An ordinary work-up afforded 33 mg (97%) of **7c** as a colorless solid, mp 62-63 °C (from hexane). *Anal.* Calcd for $C_{10}H_{19}N_2ClSSi$: C, 45.69; H, 7.29; N, 10.66. Found: C, 45.91; H, 7.43; N, 10.51.

4-Chloro-3-methyl-5-aminoisothiazole (7b). By means of the predescribed procedure, 3-methyl-5-aminoisothiazole (**4a**, 30 mg, 0.26 mmol) was converted into **7b** (38 mg, 99%) as a colorless crystalline product: mp 62-63 °C (from hexane).

Table 1. Spectral Data of Chlorides (**5a-d**, **6**, and **7a-c**).

compd	ms (m/z)	^{1}H nmr (δ, $CDCl_3$)	uv[λ_{max}, (logε)] (MeOH, nm)
5a	494 (M^+, 49%), 496 (M^++2, 61%) 498 (M^++4, 23%), and 339 (M^+-55, 100%)	-0.13 (s, 6H), 1.04 (s, 9H), 5.02 (br s, 1H), 7.15 (s, 1H), 7.33, 7.55 (ABq, J = 8 Hz, 4H), and 7.37, 7.77 (ABq, J = 9 Hz, 4H)	344 (4.28), 273 (4.55)
5b	426 (M^+, 59%), 428 (M^++2, 30%), and 369 (M^+-57, 100%)	-0.12 (s, 6H), 1.07 (s, 9H), 5.08 (br s, 1H), 7.17 (s, 1H), and 7.2-8.1 (m, 10H)	
5c	410 (M^+, 39%), 412 (M^++2, 17%), and 353 (M^+-57, 100%)	-0.19 (s, 6H), 0.98 (s, 9H), 5.02 (br s, 1H), and 7.3-8.0 (m, 10H)	
5d	380 (M^+, 100%) and 382 (M^++2, 92%)	4.57 (br s, 2H), 7.15 (s, 1H), 7.32, 7.73 (ABq, J = 8 Hz, 4H), and 7.33, 7.50 (ABq, J = 8 Hz, 4H)	345 (3.87) 274 (4.26)
6	528 (M^+, < 5%), 530 (M^++2, < 10%), and 439 (M^+-89, 100%)	-0.10 (s, 6H), 0.96 (s, 9H), 7.40 (s, 4H), 7.48, 7.94 (ABq, J = 9 Hz, 4H), and 7.98 (s, 1H)	282 (4.13) 245 (4.39)
7a	262 (M^+, 23%), 264 (M^++2, 10%), and 205 (M^+-57, 100%)	0.26 (s, 6H), 0.92 (s, 9H), 2.27 (s, 3H), and 4.1-4.5 (br s, 1H)	
7b	148 (M^+, 100%) and 150 (M^++2, 39%)	2.37 (s, 3H) and 4.2-4.8 (br s, 2H)	
7c	243 (M^+, 100%) and 245 (M^++2, 66%)	2.52 (s, 3H) and 7.39, 7.80 (ABq, J = 9 Hz, 4H)	

Anal. Calcd for $C_4H_5N_2ClS$: C, 32.23; H, 3.39; N, 18.85. Found: C, 32.62; H, 3.47; N, 18.87.

4-Chloro-3-*p*-chlorophenyl-5-methylisothiazole (7a). A mixture of 3-*p*-chlorophenyl-5-methylisothiazole (**2a**) (20 mg, 0.095 mmol) and 13 mg (0.097 mmol) of *N*-chlorosuccinimide was allowed to react at room temperature for 2 days. After work-up and tlc separation on silica gel (hexane-ether; 85 : 15), 8 mg of **2a** was recovered and 13 mg (57%) of **7a** was obtained as colorless oil.

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