Study on the Strucrures of 2-Substituted Iminothiazolidine Derivatives

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The reaction of 2-bromoethylamine **1** with methylisothiocyanate **2** under mild condition gave 2-methylamino-2-thiazoline **3** as the major product together with two kinds of byproducts, 3-(*N*-methylthiocarbamoyl)-2-methyliminothiazolidine **4** and *N,N'*-dimethyl-*N*-(2-thiazolin-2-yl)thiourea **5**. Thermal isomerization of **5** to **4** was observed. The structures of the byproducts were confirmed by X-ray crystallography.

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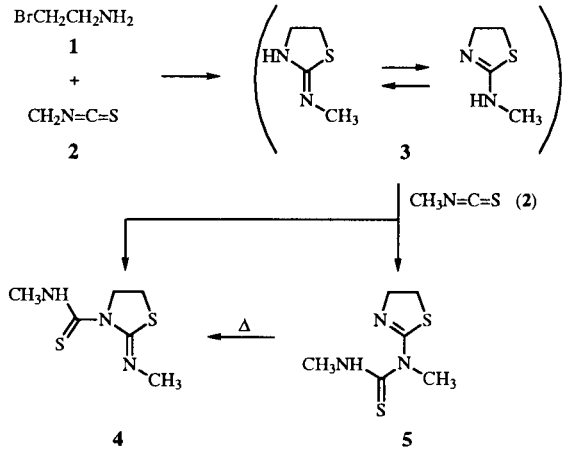
Considerable attention has been paid to 2-substituted iminothiazolidine derivatives which exhibited various biological activities, such as antiinflammatory [1-3], cardiotonic [4], antitumor [5] and other activities. These iminothiazolidines have also been important synthetic intermediates as have already been investigated by our group [6-8].

The reaction of 2-bromoethylamine **1** with methylisothiocyanate **2** is well known as an effective method to give 2-methylamino-2-thiazoline **3** through an intermolecular cyclization [9]. Gabriel [10] had already reported that the above reaction gave a byproduct (mp 70°) which was assigned to *N,N'*dimethyl-*N*-(2-thiazolin-2-yl)thiourea **5** besides **3** as the major product.

However, Yamamoto *et al.* [11] reinvestigated the Gabriel's method and got the byproduct (mp 67°) which was assigned to 3-(*N*-methylthiocarbamoyl)-2-methyliminothiazolidine **4** in terms of several spectroscopic data and an alternative synthetic route from **3** and **2**. The present paper describes clarification of the structures of byproducts obtained from the reaction of **1** and **2**.

Scheme 1



We have repeated the Gabriel's method carefully by reacting **1** with **2** to yield the byproduct (67-69°) together with **3**. Table 1 shows the physical data for this byproduct, which were in accord with those reported by Yamamoto *et al.* [11]. Moreover, the structure of this byproduct was verified by X-ray crystallography to be **4** (Tables 2, 3 and 5).

When the reaction of **1** with **2** was performed under much milder condition (under 20°), a small amount of another byproduct (mp 101-102°) (0.8%) was produced along with the said byproduct **4** (8%). The structure of the another byproduct was determined by X-ray crystallography to be **5** (Tables 2, 4 and 6). The physical data for **5** were summarized in Table 1. Refluxing **5** in benzene gave rise to **4**, while refluxing **4** in benzene did not cause any reaction to recover unchanged **4**. These results indicated that **5** was isomerized to thermodynamically more stable **4**.

In connection with these experiments, the reversed type of isomerization to the above has precedent. Yamamoto *et al.* [12] reported that 2-aminothiazoline, *N'*-desmethyl compound of **3**, reacted with **2** below 40° to give 3-(*N*-methylthiocarbamoyl)-2-iminothiazoline, *N'*-desmethyl compound of **4**, which isomerized to the thermodynamically more stable 2-(*N*-methylthiocarbamoyl)amino-2-thiazoline, the *N'*-desmethyl compound of **5**. Furthermore, Fromm *et al.* [13] and Klayman *et al.* [14] reported respectively that a similar reaction using phenylisothiocyanate afforded the type **4** compound, followed by presumably a

Scheme 2. Atomic Numbering of **4** and **5**

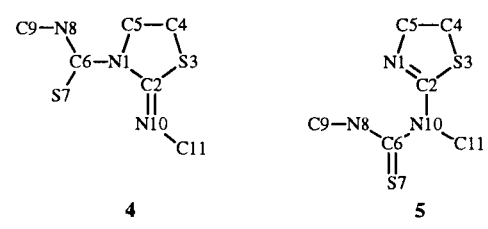


Table 1

Physical Properties of **4** and **5**

Compound No.	mp. (°C) (Ligroin)	MS m/z, relative intensity	IR (KBr disk) cm^{-1} -3000	1700-1500	-1300	-1200	^{1}H-NMR (ppm) (Chloroform-d_1)	uv λmax nm (ε) (2-Propanol)	TLC Rf value	Elemental Analysis	Calcd.	Found
4	67-69	189 (100) 116 (93) 115 (98) 74 (98) 60 (81)	3450(vw) 3230(vw) 3130(w)	1635(s) 1570(sh) 1560(s)	1460(m) 1440(m) 1400(m) 1380(s) 1345(m)	1295(s) 1255(s)	12.24 (1H, br, N-H) 4.72 (2H, t, J = 7Hz, N-CH_2 3.38-2.95 (8H, m)	240.0 (sh) 265.0 (17810)	1: 0.55 2: 0.73 3: 0.59	H C N	5.86 38.07 22.20	5.88 38.16 22.19
5	101-102	189 (77) 116 (100) 115 (66) 73 (96) 69 (97)	3425(vw) 3110(w)	1605(s) 1555(sh) 1550(s)	1450(m) 1435(m) 1415(w) 1365(s)	1290(s) 1210(w)	12.20 (1H, br, N-H) 4.23 (2H, t, J=7Hz, N-CH_2) 3.81 (3H, s, N-CH_3) 3.33 (2H, t, J = 7Hz, S-CH_2) 3.16 (3H, d, J = 5Hz, $NHCH_3$)	231.1 267.0 (16472)	1: 0.56 2: 0.72 3: 0.51	H C N	5.86 38.07 22.20	5.91 38.12 22.14

Table 2

Crystal Data of **4** and **5**

	4	**5**
Chemical formula	$C_6H_{11}N_3S_2$	$C_6H_{11}N_3S_2$
Formula weight	189.294	189.294
Crystal system	monoclinic	monoclinic
Cell dimension (Å)	a = 4.745 b = 12.039 c = 8.988 β = 116.810°	a = 12.079 b = 12.844 c = 11.946 β = 107.080°
Cell volume ($Å^3$)	458.25	1771.59
Space group	P2(1)	C2 /c
Z	2	8
Dx (g cm^{-3})	1.3719	1.4195
F (0, 0, 0)	200.00	800.00
λ (Å)	1.5418	1.5405
μ (CuKα)	47.42	49.06

Table 3

Final Atomic Coordinates and Isotropic Thermal Parameters of **4**

Atom	x	y	z	Beq ($Å^2$)
N(1)	0.515(2)	0.4935(8)	0.711(1)	4.3(3)
C(2)	0.806(2)	0.4783(9)	0.856(1)	4.2(3)
S(3)	0.9754(7)	0.3508(3)	0.8474(4)	5.48(9)
C(4)	0.626(3)	0.306(1)	0.673(2)	7.9(6)
C(5)	0.438(3)	0.405(1)	0.588(1)	5.7(4)
C(6)	0.319(2)	0.585(1)	0.681(1)	4.0(3)
S(7)	-0.0139(7)	0.5945(4)	0.4973(4)	5.8(1)
N(8)	0.406(2)	0.6630(8)	0.796(1)	4.6(3)
C(9)	0.214(3)	0.760(1)	0.787(2)	6.4(5)
N(10)	0.915(2)	0.5489(8)	0.972(1)	5.1(4)
C(11)	1.211(3)	0.522(1)	1.119(2)	6.7(6)
H(4a)	0.68(3)	0.26(2)	0.58(2)	
H(4b)	0.48(3)	0.25(2)	0.71(2)	
H(5a)	0.20(3)	0.38(1)	0.54(2)	
H(5b)	0.51(4)	0.43(2)	0.50(2)	
H(8)	0.63(3)	0.65(1)	0.91(2)	
H(9a)	0.00(3)	0.79(2)	0.69(2)	
H(9b)	0.19(4)	0.76(2)	0.90(2)	
H(9c)	0.36(3)	0.83(2)	0.80(1)	
H(11a)	1.35(4)	0.45(2)	1.14(2)	
H(11b)	1.36(4)	0.59(2)	1.13(2)	
H(11c)	1.17(4)	0.53(2)	1.23(2)	

Table 4

Final Atomic Coordinates and Isotropic Thermal Parameters of **5**

Atom	x	y	z	Beq($Å^2$)
N(1)	1.1228(2)	0.3095(2)	0.3736(2)	4.1(1)
C(2)	1.0992(2)	0.2181(2)	0.4005(2)	3.2(1)
S(3)	1.00572(8)	0.20634(7)	0.48947(8)	4.59(4)
C(4)	0.9900(3)	0.3451(3)	0.4901(3)	4.9(2)
C(5)	1.0661(3)	0.3918(2)	0.4192(3)	4.4(1)
C(6)	1.2136(2)	0.1229(2)	0.2932(2)	3.4(1)
S(7)	1.25663(7)	0.00812(6)	0.25101(8)	4.79(4)
N(8)	1.2475(2)	0.2142(2)	0.2635(2)	4.1(1)
C(9)	1.3193(3)	0.2240(3)	0.1861(3)	5.6(2)
N(10)	1.1409(2)	0.1265(2)	0.3657(2)	3.6(1)
C(11)	1.1056(3)	0.0281(3)	0.4093(3)	5.1(2)
H(4a)	1.016(3)	0.370(3)	0.577(3)	
H(4b)	0.905(3)	0.363(3)	0.453(3)	
H(5a)	1.015(3)	0.435(2)	0.346(2)	
H(5b)	1.133(2)	0.436(3)	0.482(3)	
H(8)	1.218(3)	0.276(3)	0.295(3)	
H(9a)	1.348(3)	0.165(4)	0.149(3)	
H(9b)	1.396(3)	0.263(3)	0.229(4)	
H(9c)	1.277(4)	0.263(3)	0.118(3)	
H(11a)	1.046(3)	0.015(3)	0.462(3)	
H(11b)	1.175(3)	-0.010(3)	0.452(3)	
H(11c)	1.061(3)	-0.017(3)	0.333(3)	

Table 5

Selected Bond Lengths(Å) and Angles(°) of **4**

Bond lengths

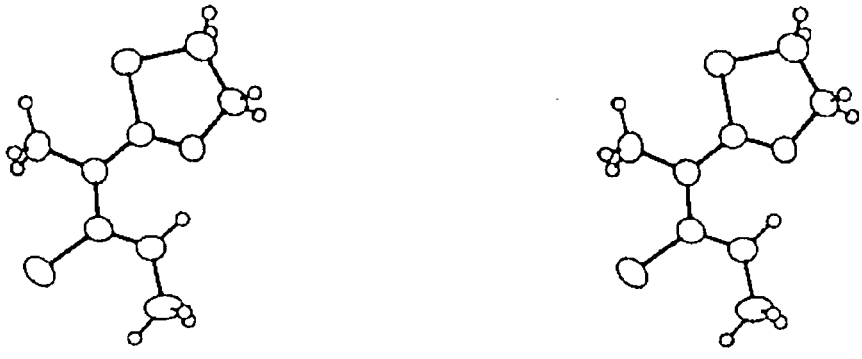
N(1) - C(2)	1.42(1)	C(4) - C(5)	1.47(2)
N(1) - C(5)	1.46(2)	C(6) - S(7)	1.70(1)
N(1) - C(6)	1.39(1)	C(6) - N(8)	1.32(2)
C(2) - S(3)	1.75(1)	N(8) - C(9)	1.46(2)
C(2) - N(10)	1.26(1)	N(10) - C(11)	1.47(2)
S(3) - C(4)	1.77(2)		

Bond Angle

C(2)-N(1)-C(5)	114.1(7)	S(3)-C(4)-C(5)	108.8(6)
C(2)-N(1)-C(6)	125.0(7)	N(1)-C(5)-C(4)	107.9(9)
C(5)-N(1)-C(6)	120.9(8)	N(1)-C(6)-S(7)	119.6(4)
N(1)-C(2)-S(3)	110.5(4)	N(1)-C(6)-N(8)	117.6(6)
N(1)-C(2)-N(10)	122.5(6)	S(7)-C(6)-N(8)	122.7(5)
S(3)-C(2)-N(10)	127.0(4)	C(6)-N(8)-C(9)	123.9(8)
C(2)-S(3)-C(4)	92.3(7)	C(2)-N(10)-C(11)	117.8(9)

Scheme 3. Stereoscopic Views of **4** and **5**

4



5

Table 6
Selected Bond Lengths(Å) and Angles(°) of **5**

Bond lengths

N(1) - C(2)	1.272(4)	C(6) - S(7)	1.688(3)
N(1) - C(5)	1.450(4)	C(6) - N(8)	1.325(4)
C(2) - S(3)	1.770(3)	C(6) - N(10)	1.404(4)
C(2) - N(10)	1.390(4)	N(8) - C(9)	1.446(5)
S(3) - C(4)	1.792(4)	N(10) - C(11)	1.476(4)
C(4) - C(5)	1.542(5)		

Bond Angle

C(2)-N(1)-C(5)	114.3(2)	S(7)-C(6)-N(8)	123.1(1)
N(1)-C(2)-S(3)	117.4(1)	S(7)-C(6)-N(10)	121.1(1)
N(1)-C(2)-N(10)	125.3(2)	N(8)-C(6)-N(10)	115.7(2)
S(3)-C(2)-N(10)	117.3(1)	C(6)-N(8)-C(9)	122.6(2)
C(2)-S(3)-C(4)	90.3(2)	C(2)-N(10)-C(6)	124.0(2)
S(3)-C(4)-C(5)	107.7(1)	C(2)-N(10)-C(11)	116.8(2)
N(1)-C(5)-C(4)	110.3(2)	C(6)-N(10)-C(11)	119.2(2)

thermal isomerization to give the type **5** compound, whose structure was confirmed by X-ray analysis [15].

In conclusion, the reaction of **1** with **2** under mild conditions gave small amounts of two byproducts **4** and **5** along with **3** as the major product. It is suggested that the reaction of **3** with **2** takes place at both the endocyclic and exocyclic nitrogen to afford two kinds of the corresponding byproducts **4** and **5**, and that **5** isomerizes to the thermodynamically more stable **4**.

EXPERIMENTAL

Melting points were determined on a Yamato MP-21 apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 260-50 spectrometer (KBr disk). The following abbreviations are used: vw = very week, w = week, sh = shoulder, s = strong and m = medium. The ^{1}H-NMR spectra were determined at 60 MHz on a Hitachi R-24B spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet and br = broad. Electron impact mass spectra were measured with a Hitachi M-80A spectrometer. The uv spectra were recorded on a Hitachi U-3200 UV-Visible recording spectrophotometer in 2-propanol. Thin-layer chromatograms were carried out on Merck 60 F_{254} silica gel fluorescent 5x10 cm slides and detected by iodine vapor. The following solvents were used: 1 = chloroform, 2 = acetone, 3 = (1:1) mixture of cyclohexane and ethyl acetate. All compounds were analyzed for C, H, N and values were within ±0.4% of theoretical values.

X-Ray Crystal Analysis.

Crystals **4** and **5** were grown from ligroin by slow evaporation at room temperature. Crystallization and data collection parameters are summarized in Table 2. The crystal system and space group were determined from oscillation and Weissenberg photographs. Cell constants were determined by a least-squares fit of 25 reflections ($20° < 2\theta < 60°$) measured with graphitemonochromated CuKα radiation on an automated Rigaku AFC-5 diffractometer. The 2θ value used for each reflection was the average of the values of the Friedel pair. Crystal densities were measured by a flotation method using an aqueous potassium iodide solution. Intensities for each crystal were collected in a similar manner with the same diffractometer. The θ -2 θ scan technique was employed. Background was counted for 5 s at the edges of each reflection. Structural deterioration during data collection was monitored by measuring four standard reflections measured at every 100 reflection intervals. Lorentz and polarization corrections were applied, but no absorption and extinction corrections were made.

The structures of **4** and **5** were solved by the direct method using the MULTAN 78 program [16] and refined by the fullmatrix least-squares method with isotropic thermal parameters, and then by the block-diagonal least-squares method with anisotropic ones. Geometrically reasonable hydrogen atom positions were determined on a difference Fourier map, and were included in subsequent refinements with an overall isotropic thermal parameter. Final atomic parameters with their standard deviations are listed in Table 3, 4, 5 and 6. The atomic numbering used is shown in Scheme 2. For all crystallographic computations, the UNICS programs [17] were used, and the atomic scattering factors were taken from the International Tables for X-Ray Crystallography [18]. The numerical calculations were performed on a Micro VAX II computer.

The Reaction of 2-Bromoethylamine **1** with Methylisothiocyanate **2**.

a) Gabriel's method.

To the benzene layer of free **1**, liberated from its HBr salt (15.13 g, 0.122 mole), 33% potassium hydroxide solution (80 ml) and benzene (80 ml), **2** (14.6 g, 0.2 mole) was added with ice cooling. The mixture was refluxed for 2.5 hours. After standing at room temperature, the reaction mixture was extracted three times with water (60 ml). The extracted aqueous layer was adjusted to *p*H 12 by the addition of 40% sodium hydroxide solution and extracted with benzene (200 ml). The benzene extract was dried with anhydrous sodium sulfate and evaporated *in vacuo* to give 2-methylamino-2-thiazoline **3** in 44% yield.

On the other hand, the benzene layer was evaporated and the residue was dissolved in 5% sulfuric acid solution and neutralized with 10% ammonia solution to precipitate 3-(*N*-methylthiocarbamoyl)-2-methyliminothiazolidine **4** in 6% yield.

b) Gabriel's Method without Heating.

The reaction described above was carried out with stirring under 20° for 4 hours. After reaction, the reaction mixture was treated as above to give **3** in 48% yield. The benzene layer was evaporated to dryness and the residue was chromatographed on silica gel with mixture of *n*-hexane and ethyl acetate (1:1) as eluent to give **4** in 8% yield and *N,N'*-dimethyl-*N*-(2-thiazolin-2-yl)thiourea **5** in 0.8% yield respectively. Each product was recrystallized from ligroin.

The Reaction of **3** with **2**.

Compound **3** (1.16 g, 0.01 mole) was dissolved in benzene (20 ml) and to the benzene solution was added a drop of **2** (0.73 g, 0.01 mole) under 20°. The mixture was refluxed for 3 hours. After standing at room temperature for 2 hours, the reaction mixture was evaporated to dryness and the residue was recrystallized from ligroin to give **4** in 53% yield.

Thermal Isomerization of **5** and **4**.

A benzene solution (15 ml) including **5** (0.1 g, 0.53 mmole) was heated under refluxing for 5 hours. After cooling the reaction solution was evaporated *in vacuo*. The residue was recrystallized from ligroin to give **4** in almost quantitative yield, which was identical with the authentic sample **4**.

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