

**Thiocyanations. 4. Cyclization of 1-Isothiocyanato-2-thiocyanates.  
A Stereospecific Route to the Preparation of 4,5-Thiazolidine-2-thiones<sup>1,2</sup>**

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When 1-isothiocyanato-2-thiocyanates **2** are heated in ethanolic potassium hydroxide, they cyclize to 4,5-thiazolidine-2-thiones. It was found that 4,5-thiazolidine-2-thiones prepared in this manner are formed stereospecifically. The representative examples of adducts **2** cyclized to the heterocyclic derivatives are discussed and a mechanism based on the experimental observations is proposed.

*vic*-Dithiocyanates **1**, which are obtained by the trans addition<sup>4,5</sup> of thiocyanogen to olefins (eq 1), have long been useful intermediates for the preparation of thiiranes<sup>6</sup> **3** (eq 2) and, more recently, were effectively cyclized to 2-imino-1,3-dithiolane salts **4** (eq 3).<sup>2</sup> The isomeric adduct, 1-isothiocyanato-2-thiocyanate **2**, has been identified and isolated as a minor product of the thiocyanation reaction.<sup>4,7</sup> However, studies in this laboratory<sup>8</sup> have shown that the relative

amounts of the two isomers **1** and **2** formed are solvent dependent so that either isomer may be prepared as the primary product (eq 1). The versatility of this reaction provides isomer **2** as a potential intermediate which could extend the utility of the thiocyanation reaction to other heterocyclic preparations.

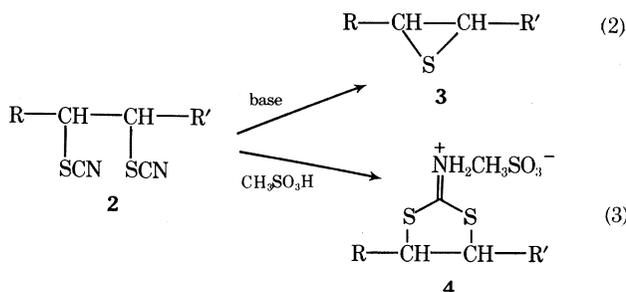
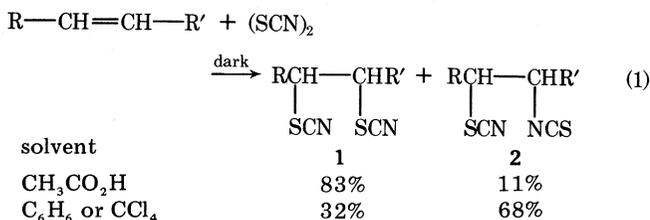
In contrast to the known base-induced cyclization of *vic*-dithiocyanates to form the three-membered thiirane ring<sup>6</sup> (eq

Table I. Yields and Stereochemistry of Thiazolidine-2-thiones from 1-Isothiocyanato-2-thiocyanates

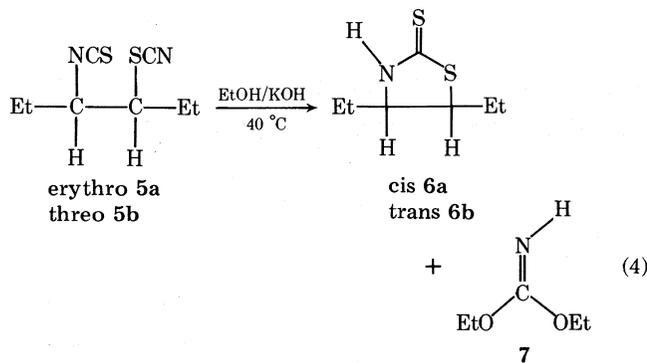
$\begin{array}{c} \text{SCN} \quad \text{SCN} \\   \quad   \\ \text{R}-\text{CH}-\text{CHR}' \end{array}$	R	R'	$\begin{array}{c} \text{S} \\    \\ \text{HN}-\text{C}-\text{S} \\   \quad   \\ \text{R}-\text{CH}-\text{CH}-\text{R}' \end{array}$	Yield, %
5a erythro	CH <sub>3</sub> CH <sub>2</sub> -	CH <sub>3</sub> CH <sub>2</sub> -	6a cis	70
5b threo	CH <sub>3</sub> CH <sub>2</sub> -	CH <sub>3</sub> CH <sub>2</sub> -	6b trans	60
8 <sup>a</sup>	C <sub>4</sub> H <sub>9</sub> -	H	9a	85 } 85 15
	H-	C <sub>4</sub> H <sub>9</sub> -	9b	
10 trans		-C <sub>4</sub> H <sub>8</sub> -	11 trans	60
12 erythro	C <sub>6</sub> H <sub>17</sub> -	C <sub>6</sub> H <sub>17</sub> -	13 cis	90
14 erythro	Ph	CH <sub>3</sub>	15 cis	30
16	-(CH <sub>2</sub> ) <sub>8</sub> CO <sub>2</sub> H	H	17	50
18 erythro	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> -	-(CH <sub>2</sub> ) <sub>7</sub> CO <sub>2</sub> H	19 cis	60
20 threo	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> -	-(CH <sub>2</sub> ) <sub>7</sub> CO <sub>2</sub> H	21 trans	45

<sup>a</sup> 8 was an unseparable mixture of two positional isomers; however, the products of cyclization were separated to pure 9a and 9b.

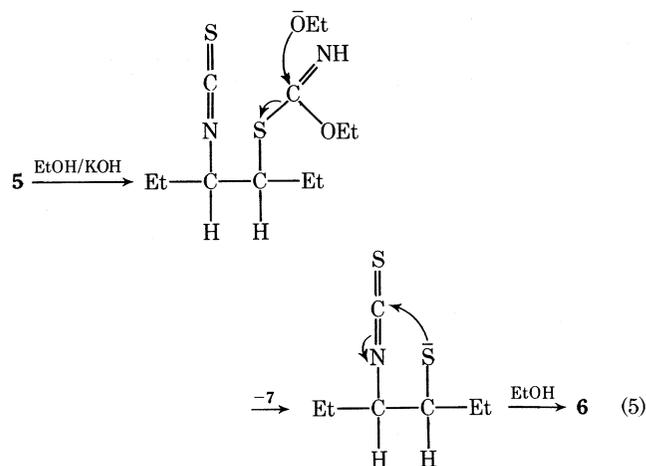
2), we have found that 1-isothiocyanato-2-thiocyanate adducts 2 cyclize in base to form the five-membered heterocycle 4,5-



thiazolidine-2-thione 6 as formulated in eq 4 for the erythro adduct 5a and threo adduct 5b. Diethyl imidocarbonate 7 was

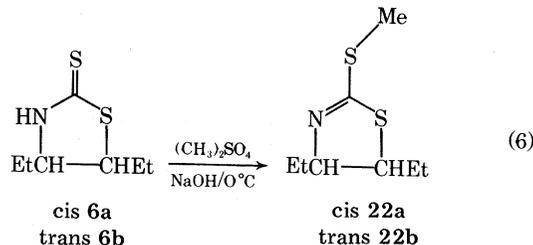


also isolated as the coproduct of this reaction and was identified by IR and NMR spectra and by comparison of its GLC retention time with that of an authentic sample prepared by an independent method.<sup>9a,b</sup> The isolation of coproduct 7 aided in establishing a mechanism for the cyclization of 5a and 5b. In the proposed mechanism shown in eq 5 initial attack by base on 5 occurs at the thiocyanate group and does not involve the asymmetric methine carbon atoms whose stereochemical identity is maintained in the product 6. A series of aliphatic 4,5-thiazolidine-2-thiones listed in Table I was obtained in yields ranging from 45 to 90%, whereas the aromatic adduct



14 provided the corresponding 15 less efficiently.

Proof of structure of the geometric isomers 6a and 6b was aided by the earlier study of Foglia et al.,<sup>10</sup> who synthesized the two compounds by an alternate procedure. They demonstrated with <sup>1</sup>H NMR spectroscopy that 6a, the isomer with the larger methine coupling constant (*J*<sub>ab</sub> = 6.8 Hz), was the cis isomer and that 6b (*J*<sub>ab</sub> = 4.2 Hz) was the trans isomer. Our IR and NMR spectra for these isomers agreed with those of Foglia; hence, the geometry of 6a and 6b was established. However, spectral comparison does not rule out the possibility of contamination of each isomer by small amounts of its geometric isomer. To establish the stereospecificity of the cyclization reaction, the crude reaction products 6a and 6b, from the cyclization of 5a and 5b, were each converted to the 2-methylthio-Δ<sup>2</sup>-thiazoline derivative (eq 6). This sequence does



not alter the stereochemistry at the asymmetric carbon atoms of 6a and 6b so that no change in geometric configuration should occur in this reaction. The thiazoline derivatives 22a and 22b were obtained as volatile liquids. Each product was examined without further purification to prevent changes in composition during workup. It has been reported<sup>11</sup> that the IR spectra of thiazolines display an intense absorption at 1575

$\text{cm}^{-1}$  which is ascribed to the  $\text{C}=\text{N}$  linkage of the thiazoline ring. The IR spectra of **22a** and **22b** showed this absorption. Foglia et al.<sup>10</sup> have reported that the GLC characteristics of isomeric thiazolines are analogous to those of the corresponding isomeric oxazolines<sup>12</sup> wherein the *cis* isomers for both series have longer relative retention times than the *trans* isomers. The crude products **22a** and **22b** were analyzed by GLC and each was found entirely free of the opposite geometric isomer. This indicates complete stereospecific cyclization of the precursors **5a** and **5b** to the thiazolidine-2-thiones **6a** and **6b**, respectively. From these results it may be inferred that the proposed *trans* addition of thiocyanogen to olefins in formation of 1-isothiocyanato-2-thiocyanates<sup>4,5</sup> is verified.

The cyclization of **5a** and **5b** to form **6a** and **6b** appears to be the only reported method for the stereospecific synthesis of both *cis*- and *trans*-thiazolidine-2-thiones. Other reports<sup>10,13</sup> indicate that while the *trans*-thiazolidine-2-thione may be obtained free of the *cis* isomer, the formation of the *cis* compound is accompanied by no less than 8% of the *trans* isomer.

### Experimental Section

Melting points (uncorrected) were determined on a Kofler hot stage.<sup>14</sup> Infrared spectra were measured with a Perkin-Elmer Model 457 grating spectrophotometer. NMR spectra were recorded on a Jeolco C-60H spectrometer. Mass spectra were obtained with a Du Pont Model 21492 mass spectrometer. GLC analyses were carried out with an F&M Model 810 gas chromatograph.

**Materials.** *cis*- and *trans*-3-hexene and 1-phenylpropene were obtained from Chemical Samples Co., and their purity was established by GLC. 1-Hexene and cyclohexene were Phillips Petroleum products and were found to be 99+% pure. 10-Hendecenoic acid and *trans*-9,10-octadecenoic acid were prepared in this laboratory. Methyl *cis*-9,10-octadecenoate (99% purity) was purchased from Applied Science Labs. All solvents used in this study were reagent grade.

**Preparation and Purity of 1-Isothiocyanato-2-thiocyanates.** The procedures used to prepare these adducts have been reported elsewhere.<sup>4,8</sup> All of the 1-isothiocyanato-2-thiocyanates prepared were isolated from the product mixtures by silica gel chromatography as amber-colored, viscous oils. Analysis of these compounds by GLC confirmed their stereochemical purity. The IR spectra of these compounds are characterized by the intense absorption at  $2150\text{ cm}^{-1}$  ( $\nu$ ) for  $-\text{SCN}$  and at  $2060\text{ cm}^{-1}$  (broad) for  $-\text{NCS}$ . A detailed analysis of the  $^1\text{H}$  NMR spectra of **5a** and **5b** will be published elsewhere.<sup>5</sup>

**Cyclization of 1-Isothiocyanato-2-thiocyanates.** The 1-isothiocyanato-2-thiocyanate adduct (15 mmol) and KOH (2.0 g) in absolute ethanol (35 mL) were heated at  $45^\circ\text{C}$  for 45 min. The reaction mixture was acidified with dilute HCl, extracted with  $\text{CHCl}_3$ , and dried over  $\text{Na}_2\text{SO}_4$ . After removal of solvent, the residue was purified by silica gel chromatography. The purity of samples, excluding **17**, **19**, and **21**, was determined by GLC.

***cis*-4,5-Diethylthiazolidine-2-thione (6a)** from *erythro*-3-isothiocyanato-4-thiocyanatohexane (**5a**) was isolated as a viscous oil. The product was identified by comparison of the IR and NMR spectra of the authentic compound prepared by an alternate procedure,<sup>10</sup> and by the preparation of the 3-*p*-nitrobenzoyl-*cis*-4,5-diethylthiazolidine-2-thione derivative, mp  $93\text{--}94^\circ\text{C}$  (lit.<sup>10</sup>  $93\text{--}94^\circ\text{C}$ ).

***trans*-4,5-Diethylthiazolidine-2-thione (6b)** was obtained from *threo*-3-isothiocyanato-4-thiocyanatohexane (**5b**), and identified by comparison of its melting point,  $58.5\text{--}59.5^\circ\text{C}$  (lit.<sup>10</sup>  $59\text{--}60^\circ\text{C}$ ), NMR, IR, and mass spectra with those of the authentic compound prepared by an alternate procedure.<sup>10</sup>

**4-Butylthiazolidine-2-thione (9a) and 5-butylthiazolidine-2-thione (9b)** were obtained from 1(2)-isothiocyanato-2(1)-thiocyanate (**8**). The adduct **8** was a mixture of two isomeric isothiocyanatothiocyanates. GLC of the product **9** showed two overlapping peaks in the ratio 85/15. Chromatography on a silica gel column completely separated the two components **9a** and **9b**, although an insufficient amount of **9b** was obtained for a satisfactory elemental analysis: **9a** mp  $55\text{--}56^\circ\text{C}$ ; **9b** mp  $89\text{--}90^\circ\text{C}$ ; **9a** NMR ( $\text{CDCl}_3$ ) 9.3 (very broad, 2), 4.3 (broad, apparent pentuplet, 1), 3.6 and 3.2 (8 lines, 2), 2.4 (t, 2), and 1.3 ppm (s, 14); **9b** NMR ( $\text{CDCl}_3$ ) gave spectrum similar to that of **9a** except that the methine protons superimposed upon the methylene protons (3.5–4.2 ppm, 3). **9a** Anal. Calcd for  $\text{C}_7\text{H}_{13}\text{NS}_2$ :

C, 47.96; H, 7.48; N, 7.48; S, 36.58. Found: C, 47.92; H, 7.93; N, 7.65; S, 36.94.

***trans*-Hexahydrobenzothiazolidine-2-thione (11)** was obtained from *trans*-1-isothiocyanato-2-thiocyanatocyclohexane (**10**), and isolated as a solid which on recrystallization from benzene gave platelets, mp  $174\text{--}175^\circ\text{C}$  (lit.<sup>15</sup>  $173\text{--}174^\circ\text{C}$ ).

***cis*-4,5-Diethylthiazolidine-2-thione (13)** from *erythro*-9-isothiocyanato-10-thiocyanatooctadecane (**12**) was recovered as a viscous oil. The IR and NMR spectra were identical with those obtained from the authentic compound.<sup>10</sup>

***cis*-5-Methyl-4-phenylthiazolidine-2-thione (15)** from *erythro*-1-isothiocyanato-2-thiocyanato-1-phenylpropane (**14**) was isolated as a solid and recrystallized from methylene chloride/benzene: mp  $159.8\text{--}160.0^\circ\text{C}$ ; IR (KBr) 3100 (NH), 1490 (CSNH), 1250, 1030 ( $\text{C}=\text{S}$ ), 810,  $690\text{ cm}^{-1}$ . Anal. Calcd for  $\text{C}_{10}\text{H}_{11}\text{NS}_2$ : C, 57.38; H, 5.30; N, 6.69; S, 30.63. Found: C, 57.60; H, 5.46; N, 6.52; S, 29.97.

**4-(8-Carboxyooctyl)-thiazolidine-2-thione (17)** from 10-isothiocyanato-11-thiocyanatohendecanoic acid (**16**) (isomeric purity not established) was recovered as a solid and recrystallized from hexane/ether: mp  $100\text{--}102^\circ\text{C}$ ; IR (KBr) 3230 (NH), 1695 ( $\text{C}=\text{O}$ ), 1505 (CSNH), 1180, 1045 ( $\text{C}=\text{S}$ ), 950,  $840\text{ cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ ) methine resonance (4.3 ppm), methylene (3.6 and 3.2). Anal. Calcd for  $\text{C}_{12}\text{H}_{21}\text{NO}_2\text{S}_2$ : C, 52.33; H, 7.68; N, 5.09; S, 23.28. Found: C, 52.53; H, 7.93; N, 4.94; S, 23.06.

***cis*-4(5)-Octyl-5(4)-(7-carboxy)heptylthiazolidine-2-thione (19)** was obtained from *erythro*-9(10)-isothiocyanato-10(9)-thiocyanatooctadecanoic acid (**18**). The adduct **18** was a mixture of two positional isomers whose composition remained unchanged in the product **19**. The product was a solid which was recrystallized from acetone/hexane: mp  $109\text{--}111^\circ\text{C}$ ; neut equiv, calcd, 373.6, found, 370; IR (KBr) 3100 (NH), 1700 ( $\text{C}=\text{O}$ ), 1495 (CSNH), 1175, 1010 ( $\text{C}=\text{S}$ ),  $810\text{ cm}^{-1}$ . Anal. Calcd for  $\text{C}_{19}\text{H}_{35}\text{NO}_2\text{S}_2$ : C, 61.08; H, 9.44; N, 3.74; S, 17.16. Found: C, 61.05; H, 9.73; N, 3.72; S, 17.20.

***trans*-4(5)-Octyl-5(4)-(7-carboxy)heptylthiazolidine-2-thione (21)** was obtained from *threo*-9(10)-isothiocyanato-10(9)-thiocyanatooctadecanoic acid (**20**). The adduct **20** was a mixture of two positional isomers whose composition remained unchanged in the product **21**. The product was a solid recrystallizable from acetone/hexane: mp  $79\text{--}80^\circ\text{C}$ ; neut equiv, calcd 373.6, found 370; IR (KBr) 3100 (NH), 1700 ( $\text{C}=\text{O}$ ), 1495 (CSNH), 1160, 1000 ( $\text{C}=\text{S}$ ), 875,  $715\text{ cm}^{-1}$ . Anal. Calcd for  $\text{C}_{19}\text{H}_{35}\text{NO}_2\text{S}_2$ : C, 61.08; H, 9.44; N, 3.74; S, 17.16. Found: C, 61.00; H, 9.50; N, 3.74; S, 17.44.

**Diethyl imidocarbonate** was prepared by the procedure described by Nef<sup>9a</sup> using bromocyanogen and potassium hydroxide in ethanol at  $0^\circ\text{C}$ : IR ( $\text{CH}_2\text{Cl}_2$ ) 3340, 3365 (NH), 1650 ( $\text{C}=\text{N}$ ), 1080, and  $1025\text{ cm}^{-1}$ . The IR spectrum agreed with that obtained for **7**. Identical results were also obtained by comparison of the NMR spectra<sup>9b</sup> and GLC retention times of both samples.

**2-Methylthio-*cis*-4,5-diethyl-2-thiazoline (22a)** was prepared from *cis*-thiazolidine **6a** in accordance with the published procedure.<sup>10</sup> The IR spectrum of the crude reaction product was in complete agreement with the published values.<sup>10</sup> GLC analysis of this sample showed only one component.

**2-Methylthio-*trans*-4,5-diethyl-2-thiazoline (22b)** was prepared from *trans*-thiazolidine **6b** and dimethyl sulfate as described above. The IR spectrum agreed with the published values. GLC analysis of this sample showed one component having a shorter retention time than that of *cis* **22a**.

**Registry No.**—**5a**, 61522-02-9; **5b**, 61522-01-8; **6a**, 27787-21-9; **6b**, 27932-05-4; **8** isomer 1, 61522-04-1; **8** isomer 2, 61522-37-0; **9a**, 61522-38-1; **9b**, 61522-39-2; **10**, 61522-40-5; **11**, 61522-41-6; **12**, 50843-80-6; **13**, 27787-27-5; **14**, 60211-99-6; **15**, 61522-42-7; **16**, 61522-43-8; **17**, 61522-44-9; **18** isomer 1, 61522-45-0; **18** isomer 2, 61522-46-1; **19** isomer 1, 61522-47-2; **19** isomer 2, 61522-48-3; **20** isomer 1, 61522-49-4; **20** isomer 2, 61522-50-7; **21** isomer 1, 61522-51-8; **21** isomer 2, 61522-52-9; **22a**, 27787-25-3; **22b**, 27787-22-0; diethyl imidocarbonate, 2812-77-3.

### References and Notes

- (1) Presented at the 9th Middle Atlantic Regional Meeting of the American Chemical Society, Wilkes-Barre, Pa., April 23–26, 1974.
- (2) Part 3: R. J. Maxwell and L. S. Silbert, *J. Org. Chem.*, preceding paper in this issue.
- (3) Agricultural Research Service, U.S. Department of Agriculture.
- (4) L. S. Silbert, J. R. Russell, and J. S. Showell, *J. Am. Oil Chem. Soc.*, **50**, 415 (1973).
- (5) Part 5: R. J. Maxwell, P. E. Pfeffer, and L. S. Silbert, *J. Org. Chem.*, following paper in this issue.

- (6) M. Sander, *Chem. Rev.*, **66**, 297 (1966).
- (7) R. G. Guy, R. Bonnett, and D. Lanigan, *Chem. Ind. (London)*, 1702 (1969).
- (8) Part 2: R. J. Maxwell, L. S. Silbert, and J. R. Russell, *J. Org. Chem.*, accompanying paper in this issue.
- (9) (a) J. U. Nef, *Ann. Chim. (Paris)*, **287**, 265 (1895); (b) A. Schmidpeter and W. Zeiss, *Chem. Ber.*, **104**, 1199 (1971).
- (10) T. A. Foglia, L. M. Gregory, G. Maerker, and S. F. Osman, *J. Org. Chem.*, **36**, 1068 (1971).
- (11) W. Otting and F. Drawert, *Chem. Ber.*, **88**, 1469 (1955).
- (12) T. A. Foglia, L. M. Gregory, and G. Maerker, *J. Org. Chem.*, **35**, 3779 (1970).
- (13) C. S. Dewey and R. A. Bafford, *J. Org. Chem.*, **30**, 491 (1965).
- (14) Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.
- (15) M. Mousseron, F. Winternitz, and R. Dennilauler, *C. R. Acad. Sci.*, **239**, 278 (1954).