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Cyclization of α- and β-Alkylthio-Substituted Amines Possessing Positively Charged Carbon at the Nitrogen. A New Synthetic Method for Thiazolidines, Thiomorpholines and Dihydro-1,4-benzothiazines

YOSHIHARU ISHIKAWA, YOSHIYASU TERAO, KUNIO SUZUKI, NOBORU SHIKANO and MINORU SEKIYA*

Shizuoka College of Pharmacy, 2-2-1 Oshika, Shizuoka 422, Japan

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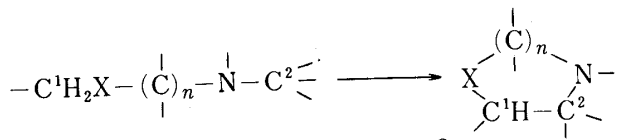
The present paper describes the finding that α- and β-alkylthio-substituted amines possessing a positively charged carbon such as =CHPh, CO_2R and CH_2SR at the nitrogen undergo cyclization in the presence of lithium diisopropylamide or sodium hydride leading to thiazolidines, thiomorpholines and dihydro-1,4-benzothiazines.

Keywords——thiazolidine; thiomorpholine; dihydro-1,4-benzothiazine; cyclization; trimethylsilyl compound; sodium hydride; lithium diisopropylamide

As are well known, existing syntheses of thiazolidine and thiomorpholine rings are mostly carried out by sulfur–carbon of nitrogen–carbon bond closure. The present paper describes syntheses based on formation of the C_4–C_5 bond of thiazolidines and C_2–C_3 bond of thiomorpholines, as depicted in the following scheme. Few such reactions have appeared in the literature.

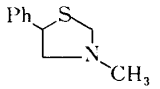
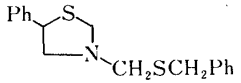
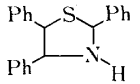
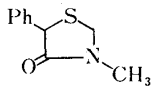
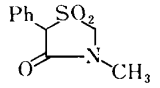
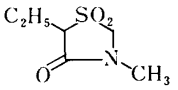
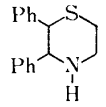
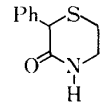
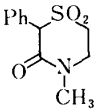


X=S or SO_2 n=1 or 2

In this scheme, where C_2 is a positively charged carbon in a group such as –N=CH–, –NCO$_2$R or >NCH$_2$SR, the reaction proceeds in the presence of sodium hydride (NaH) or lithium diisopropylamide (LDA). Mechanistically, the C_1-carbanion first formed by deprotonation attacks the C_2-carbon to form the thiazolidine or thiomorpholine ring. Our results on the production of thiazolidine and thiomorpholine derivatives are illustrated in Table I, and those on the production of dihydro-1,4-benzothiazine derivatives are given in Table II. All the reactions were carried out in tetrahydrofuran (THF) with the use of 3 molar equivalents of LDA or NaH. In particular, the formation of dihydro-1,4-benzothiazines, which is sterically much more favorable than that of thiazolidines and thiomorpholines, was almost quantitative.

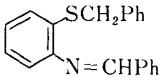
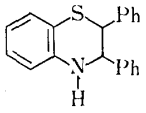
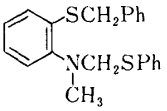
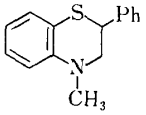
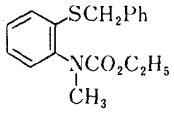
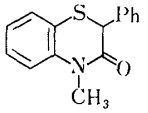
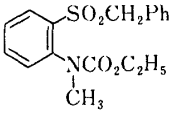
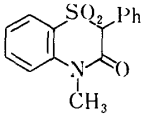
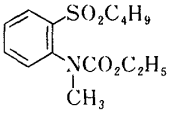
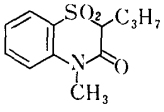
Since the reaction is initiated by the formation of a carbanion at the alkyl carbon adjacent to sulfur, easily deprotonizable *S*-benzyl is very effective for the reaction. However, alkyl sulfone analogs, among which only carbamate derivatives[1] are synthetically available, were sufficiently reactive, as can be seen in entry 6 in Table I and entry 5 in Table II. *N*-(Alkylsulfonylethyl)carbamate was exceptional, as can be seen in entry 9 in Table I, and was shown to undergo β-elimination with loss of carbamate. In spite of the inertness of *S*-alkyl

TABLE I. Syntheses of Thiazolidines and Thiomorpholines

Entry	Substrate	No.	Base	React. conditions[a] (°C)	React. conditions[a] (h)	Product	No.	Yield (%)
1	$PhCH_2SCH_2\underset{\displaystyle CH_3}{\underset{\vert}{N}}CH_2SCH_2Ph$	**1**	LDA	−70	4		**8a**	41[b]
2	$(PhCH_2SCH_2)_3N$	**2**	LDA	r.t.	28		**8b**	32[b]
3	$PhCH_2S\underset{\displaystyle Ph}{\underset{\vert}{C}}HN=CHPh$	**3**	LDA	−50	5		**8c**	24
4	$PhCH_2SCH_2\underset{\displaystyle CH_3}{\underset{\vert}{N}}CO_2C_2H_5$	**4**	LDA	−20	4		**8d**	56
5	$PhCH_2SO_2CH_2\underset{\displaystyle CH_3}{\underset{\vert}{N}}CO_2C_2H_5$	**5**	NaH	Reflux	7		**8e**	40
6	$C_3H_7SO_2CH_2\underset{\displaystyle CH_3}{\underset{\vert}{N}}CO_2C_2H_5$	**6**	NaH	Reflux	4		**8f**	56
7	$PhCH_2SCH_2CH_2N=CHPh$	**7a**	LDA	−50	5		**9a**	76
8	$PhCH_2SCH_2CH_2NHCO_2C_2H_5$	**7b**	LDA	r.t.	15		**9b**	47
9	$PhCH_2SO_2CH_2CH_2\underset{\displaystyle CH_3}{\underset{\vert}{N}}CO_2C_2H_5$	**7c**	NaH	Reflux	5		**9c**	0[c]

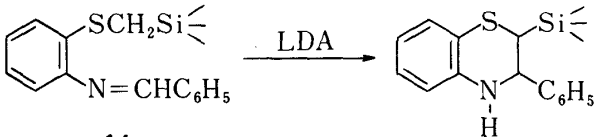
a) Solvent: THF. *b*) Yield of the hydrochloride. *c*) β-Elimination occurred to give the corresponding carbamate and olefin.

TABLE II. Synthesis of Dihydro-1,4-benzothiazines

Entry	Substrate	No.	Base	React. conditions[a] (°C)	(h)	Product	No.	Yield (%)
1		**10a**	LDA NaH	−70 Reflux	1 6		**12a, a′**	Quant.
2		**10b**	NaH	Reflux	10		**12b**	Quant.
3		**10c**	LDA	−70	3		**12c**	Quant.
4		**11a**	NaH	Reflux	4		**13a**	90
5		**11b**	NaH	Reflux	4		**13b**	95

a) Solvent: THF.

derivatives of *o*-aminothiophenol under the usual conditions, it was noticeable that the following *S*-trimethylsilylmethyl derivative reacted smoothly to give a thiomorpholine derivative possessing a trimethylsilyl grouping (which is replaceable by hydrogen) at the 2-position.



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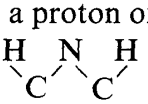
Tables III and IV contain infrared (IR) and nuclear magnetic resonance (NMR) spectral and analytical data for the starting α- and β-aminosulfide and sulfone derivatives and for the *o*-aminothiophenol derivatives, including ten new compounds, and Tables V and VI contain data for the products of the present reaction, *i.e.*, thiazolidine, thiomorpholine and dihydro-1,4-benzothiazine derivatives, most of which are unknown in the literature.

The ^{1}H-NMR spectrum of **8a** contains an AB coupling at δ 4.00 and 4.33 (J=8.9 Hz) arising from the two protons of C_2 and an ABX coupling at δ 2.47, 3.33 and 4.60 (J=11.8, 9.5 and 6.3 Hz) arising from the two protons of C_4 and a proton of C_5. In addition a long-range coupling at δ 3.33 and 4.00 (J=1.8 Hz) between a proton of C_2 and a proton of C_4 appears in this spectrum owing to the planar W shape of  of the thiazolidine ring.

Compound **8b** was isolated as its hydrochloride, which was assigned on the basis of its analytical data. Treatment with alkali gave 5-phenylthiazolidine (**8b′**), the spectral data for which are given in Table V, with ready removal of the *N*-benzylthiomethyl grouping.

TABLE III. Analytical and Spectral Data for Starting Compounds

Compound No.	bp °C (Torr) or mp °C (Recryst. solvent)	IR $\nu_{max}^{KBr\ or\ neat}$ cm^{-1}	^{1}H-NMR δ (in $CDCl_3$, J=Hz)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
1	180—182 (0.1) [lit.,[3a] bp 182—185 (0.05)]		2.36 (3H, s, NCH_3), 3.70 (4H, s, 2×$PhCH_2S$), 3.80 (4H, s, 2×SCH_2N), 7.23 (10H, s, 2×C_6H_5)				
2	43—44 (EtOH) (lit.,[3b] mp 46)		3.70 (6H, s, 3×$PhCH_2S$), 3.93 (6H, s, 3×SCH_2N), 7.24 (15H, s, 3×C_6H_5)				
3	80—81 (EtOH) (lit.,[3b] mp 67)	1630 (C=N)	3.67 (2H, s, $PhCH_2S$), 5.55 (1H, s, 7.10—7.68, 7.65—7.95 (15H, m, 3×C_6H_5), 8.28 (1H, s, N=CH)				
4	141—143 (0.6)	1706 (C=O)	1.23 (3H, t, J=7.2, CH_3), 2.85 (3H, s, NCH_3), 3.73 (2H, s, $PhCH_2S$), 4.11 (2H, q, J=7.2, OCH_2), 4.42 (2H, s, NCH_2S), 7.23 (5H, s, C_6H_5)	$C_{12}H_{17}NO_2S$	60.22 (60.18	7.16 7.14	5.85 5.91)
5	77—78 (AcOEt)	1716 (C=O) 1284 1159 (SO_2)	1.29 (3H, t, J=7.2, CH_3), 3.08 (3H, s, NCH_3), 4.18 (2H, q, J=7.2, OCH_2), 4.24 (2H, s, $PhCH_2SO_2$, 4.51 (2H, s, SO_2CH_2N), 7.32 (5H, s, C_6H_5)	$C_{12}H_{17}NO_4S$	53.12 (53.11	6.32 6.35	5.16 5.19)
6	112—113 (0.02)	1712 (C=O) 1289 1151 (SO_2)	1.15 (3H, t, J=7.3, CH_3), 1.30 (3H, t, J=7.1, $OCH_2C\underline{H}_3$), 1.69—2.11 (2H, m, C-CH_2-C), 2.89—3.06 (2H, m, SO_2CH_2), 3.16 (3H, s, NCH_3), 4.21 (2H, q, J=7.1, OCH_2), 4.53 (2H, s, SO_2CH_2N)	$C_8H_{17}NO_4S$	43.03 (43.45	7.68 7.68	6.27 6.47)
7a	155—157 (0.05)	1644 (C=N)	2.71 (2H, t, J=4.6, $SC\underline{H}_2CH_2N$), 3.68 (2H, s, $PhCH_2S$), 3.70 (2H, t, J=4.6, $SCH_2C\underline{H}_2N$), 7.17 (5H, s, C_6H_5), 7.20—7.35, 7.50—7.69 (5H, m, C_6H_5)	$C_{16}H_{17}NS$	75.25 (75.06	6.71 6.69	5.48 5.57)
7b	34—35 (EtOH)	3352 (NH) 1710 (C=O)	2.46 (2H, t, J=6.0, $SC\underline{H}_2CH_2N$), 3.32 (2H, t, J=6.0, $SCH_2C\underline{H}_2N$), 3.58 (2H, s, $PhCH_2S$), 5.03 (2H, s, OCH_2), 5.04 (1H, br, NH), 7.18 (5H, s, C_6H_5), 7.22 (5H, s, C_6H_5)	$C_{17}H_{19}NO_2S$	67.74 (68.04	6.35 6.37	4.65 4.68)
7c	201—202 (0.1)	1710 (C=O) 1310 1165 (SO_2)	1.19 (3H, t, J=7.2, CH_3), 2.88 (3H, s, NCH_3), 3.04 (2H, t, J=7.3, NCH_2), 3.62 (2H, t, J=7.3, SO_2CH_2), 4.12 (2H, q, J=7.2, OCH_2), 4.25 (2H, s, $PhCH_2SO_2$), 7.48 (5H, s, C_6H_5)	$C_{13}H_{17}NO_4S$	54.72 (54.63	6.71 6.89	4.91 4.88)

TABLE IV. Analytical and Spectral Data for Starting Compounds

Compound No.	mp °C (Recryst. solvent)	IR $\nu_{max}^{KBr\ or\ neat}$ cm^{-1}	^{1}H-NMR δ (in $CDCl_3$, J=Hz)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
10a	98—99 (EtOH)	1618 (C=N)	4.10 (2H, s, SCH_2), 6.9—7.5, 7.7—8.1 (14H, m, C_6H_4, $2\times C_6H_5$), 8.23 (1H, s, –CH=)	$C_{20}H_{17}NS$	79.17 (79.20	5.65 5.76	4.62 4.80)
10b	44—45 (Et_2O)		2.79 (3H, s, NCH_3), 3.95 (2H, s, SCH_2), 4.87 (2H, s, NCH_2), 7.13 (5H, s, C_6H_5), 6.85—7.2 (9H, m, C_6H_4, C_6H_5)	$C_{21}H_{21}NS_2$	71.75 (71.59	6.02 6.01	3.98 4.07)
10c	52—53 (Iso-Pr_2O)	1700 (C=O)	1.12 (3H, t, J=7.2, CH_3), 3.03 (3H, s, NCH_3), 3.97 (2H, s, SCH_2), 4.02 (2H, q, J=7.2, OCH_2), 6.92—7.32 (9H, m, C_6H_4, C_6H_5)	$C_{17}H_{19}NO_2S$	67.74 (67.67	6.35 6.25	4.65 4.64)
11a	49—50 (Iso-Pr_2O)	1695 (C=O) 1318 (SO_2) 1132 (SO_2)	1.24 (3H, t, J=7.2, CH_3), 3.20 (3H, s, NCH_3), 4.18 (2H, q, J=7.2, OCH_2), 5.14 (2H, s, SO_2CH_2), 7.10 (5H, s, C_6H_5), 7.17—7.87 (4H, m, C_6H_4)	$C_{17}H_{19}NO_4S$	61.24 (61.24	5.74 5.73	4.20 4.13)
11b	Oil	1724 (C=O) 1324 (SO_2) 1154 (SO_2)	0.70—1.95 (10H, m, $2\times CH_3$, $-CH_2CH_2-$), 3.18 (2H, t, J=7.8, SO_2CH_2), 3.21 (3H, s, NCH_3), 4.14 (2H, q, J=7.2, OCH_2), 7.18—8.12 (4H, m, C_6H_4)	$C_{14}H_{21}NO_4S$	56.16 (55.60	7.07 6.89	4.68 4.78)
14	95—97 (EtOH)	1624 (C=N)	0.19 (9H, s, $Si(CH_3)_3$), 2.08 (2H, s, SCH_2Si), 6.50—7.50, 7.60—7.95 (4H, m, C_6H_4), 8.29 (1H, s, CH=N)	$C_{17}H_{21}NSSi$	68.17 (67.95	7.07 6.88	4.68 4.72)

TABLE V. Thiazolidines and Thiomorpholines

Compound No.	bp °C (Torr) or mp °C (Recryst. solvent)	IR $\nu_{max}^{KBr\ or\ neat}$ cm^{-1}	^{1}H-NMR δ (in $CDCl_3$, J=Hz)	^{13}C-NMR δ (in $CDCl_3$)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
8a	186—187[a] (EtOH)		2.38 (3H, s, NCH_3), 2.47 (1H, dd, J=11.8, 9.5 C_4–H_A), 3.33 (1H, ddd, J=11.8, 6.3, 1.8, C_4–H_B), 4.33 (1H, d, J=8.9, C_2–H_A), 4.00 (2H, dd, J=8.9, 1.8, C_2–H_B), 4.60 (1H, dd, J=9.5, 6.3, PhCH), 7.12—7.44 (5H, m, C_6H_5)	41.56 (q) 51.09 (d) 64.04 (t) 69.03 (t)	$C_{10}H_{14}ClNS$[b]	55.67 (55.53	6.54 6.59	6.49 6.52)
8b′		3310 (NH)	2.12 (1H, br, NH), 3.02 (1H, dd, J=12.5, 6.1, C_4–H_A), 3.53 (1H, dd, J=12.5, 6.4, C_4–H_B), 4.2—4.6 (1H, m, C_5–H), 7.12—7.30 (5H, m, C_6H_5)	55.32 (d) 57.00 (t) 61.98 (t)				
8c	112—113 (EtOH)	3340 (NH)	2.75 (1H, br, NH), 4.36 (1H, d, J=9.0, C_4–H) 4.76 (1H, d, J=9.0, C_5–H), 6.07 (1H, s, C_2–H) 7.18—8.79 (15H, m, 3×C_6H_5)	63.72 (d) 71.68 (d) 77.26 (d)	$C_{21}H_{19}NS$	79.46 (79.31	6.03 6.38	4.41 4.32)
			2.75 (1H, br, NH), 4.35 (1H, d, J=7.1, C_4–H) 4.80 (1H, d, J=7.1, C_5–H), 5.89 (1H, s, C_2–H) 7.18—8.79 (15H, m, 3×C_6H_5)	63.50 (d) 70.99 (d) 74.44 (d)				
8d	142—144 (0.3)	1682 (C=O)	2.75 (3H, s, NCH_3), 4.11 (1H, d, J=7.8, C_2–H_A), 4.23 (1H, d, J=7.8, C_2–H_B), 4.75 (1H, s, C_5–H), 7.17—7.33 (5H, m, C_6H_5)	31.42 (q) 47.41 (t) 50.44 (d) 171.05 (s)	$C_{10}H_{11}NOS$	62.15 (62.21	5.74 5.77	7.25 7.24)
8e	158—158.5 (EtOH)	1713 (C=O) 1324 (SO_2) 1169 (SO_2)	3.16 (3H, s, NCH_3), 4.47 (1H, d, J=10.7, C_2–H_A), 4.65 (1H, d, J=10.7, C_2–H_B), 4.82 (1H, s, PhCH), 7.31—7.40 (5H, m, C_6H_5)	31.37 (q) 66.64 (d) 67.94 (t) 146.71 (s)	$C_{10}H_{11}NO_3S$	53.32 (53.52	4.92 5.00	6.22 6.28)
8f	122—123 (0.3)	1665 (C=O) 1321 (SO_2) 1135 (SO_2)	1.12 (3H, t, J=7.1, CH_3), 1.93—2.28 (2H, m, $-CH_2CH_3$), 3.06 (3H, s, NCH_3), 3.47 (1H, dd, J=5.8, 5.9, C_5–H), 4.54 (1H, d, J=10.74, C_2–H_A), 4.34 (1H, d, J=10.74, C_2–H_B)	11.32 (q) 19.07 (t) 30.83 (q) 61.98 (d) 68.21 (t) 165.57 (s)	$C_6H_{11}NO_3S$	40.66 (40.51	6.26 6.01	7.90 7.99)
9a	88—89 (EtOH)	3334 (NH)	1.90 (1H, br, NH), 3.98 (2H, s, –CH–CH–), 2.44—3.46 (4H, m, $-CH_2-CH_2-$), 7.05 (10H, s, 2×C_6H_5)	20.23 (t) 48.76 (t) 51.80 (d) 69.24 (d)	$C_{16}H_{17}NS$	75.25 (75.06	6.71 6.72	5.48 5.58)
9b	153—154 (EtOH)	1660 (C=O)	2.73—2.87 (2H, m, C_5–H), 3.49—3.66 (2H, m, C_6–H_2), 4.63 (1H, s, C_2–H), 7.25—7.50 (5H, m, C_6H_5), 7.60 (1H, br, NH)	25.36 (t) 44.10 (t) 46.60 (d) 169.80 (s)	$C_{10}H_{11}NOS$	62.15 (62.31	5.74 5.76	7.25 7.26)

a) Melting point of the hydrochloride. *b*) Analytical data for the hydrochloride.

TABLE VI. Dihydro-1,4-benzothiazines

Compound No.	mp (°C) (Recryst. solvent)	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR δ (in $CDCl_3$, J=Hz)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
12a (*cis*)	166—167 (EtOH)	3428 (NH)	4.10 (1H, br, NH), 4.30 (1H, d, J=3, S–CH), 4.91 (1H, d, J=3, N–CH), 6.35—7.05 (14H, m, 2×C_6H_5, C_6H_4)	$C_{20}H_{17}NS$	79.17 (79.00	5.65 5.69	4.61 4.86)
12a′ (*trans*)	152—153 (EtOH)	3393 (NH)	4.16 (1H, d, J=9, S–CH), 4.25 (1H, br, NH), 4.55 (1H, d, J=9, N–CH), 6.80—7.14 (14H, m, 2×C_6H_5, C_6H_4)	$C_{20}H_{17}NS$	79.17 (79.48	5.65 5.68	4.61 4.71)
12b	68—69 (EtOH)		2.91 (3H, s, NCH_3), 3.55 (2H, d, N–CH_2), 4.36 (1H, t, S–CH), 6.53—7.34 (9H, m, C_6H_5, C_6H_4)	$C_{15}H_{15}NS$	74.65 (74.70	6.26 6.25	5.80 5.83)
12c	153—154 (EtOH)	1680 (C=O)	3.48 (3H, s, NCH_3), 4.63 (1H, s, S–CH), 6.90—7.45 (9H, m, C_6H_5, C_6H_4)	$C_{15}H_{13}NOS$	70.56 (70.17	5.13 5.19	5.49 5.49)
13a	168—169 (AcOEt)	1684 (C=O) 1322 1162 (SO_2)	3.55 (3H, s, NCH_3), 5.14 (1H, s, SO_2–CH), 6.68—7.92 (9H, m, C_6H_5, C_6H_4)	$C_{15}H_{13}NO_3S$	62.70 (62.73	4.56 4.66	4.87 4.91)
13b	109—110 (Iso-Pr_2O)	1680 (C=O) 1314 1172 (SO_2)	0.92 (3H, t, ω–CH_3), 1.10—2.19 (4H, m, –CH_2CH_2–), 3.43 (3H, s, NCH_3), 3.89 (1H, dd, J=7.2, 7.8, SO_2CH), 7.05—7.92 (4H, m, C_6H_4)	$C_{12}H_{15}NO_3S$	56.90 (57.09	5.97 6.03	5.53 5.55)
15	67—69 (MeOH)	3378 (NH)	−0.18 (9H, s, $Si(CH_3)_3$), 2.70 (1H, d, J=8.8, S–CH), 4.45 (1H, d, J=8.8, N–CH), 3.97 (1H, s, NH), 6.30—7.15 (4H, m, C_6H_4), 7.30 (5H, s, C_6H_5)	$C_{17}H_{21}NSSi$	68.17 (67.91	7.07 7.03	4.68 4.66)

Compound **8c** was regarded as a mixture of two stereoisomers from its ^{1}H-NMR and ^{13}C-NMR spectral data. However, attempts to separate them failed. On the assumption that the two bulky phenyls at C_4 and C_5 exist in *trans*-configuration [coupling constants (9.0 Hz and 7.1 Hz) between the C_4 and C_5 protons of the two isomers do not differ greatly], these two isomers may be assigned as *cis* and *trans* with respect to the two phenyls at C_2 and C_4 or C_5.

The product[2] obtained from **10a** was separated into two isomers, **12a** and **12a′**, by fractional recrystallization from ethanol. The ratio of the two isomers was estimated to be about 1 : 1 by calculation based on the ^{1}H-NMR signals of the mixture. Table VI contains spectral data for these *cis* and *trans* isomers with respect to C_2 and C_3 configuration. The isomer **12a′**, possessing a much larger value (J=9 Hz) of coupling constant at δ 4.16 and 4.55 relative to that of **12a** (J=3 Hz) at δ 4.30 and 4.91, is regarded as the *trans* isomer based on the Karplus theory, since the plane angle of the C–H bonds of the *trans* isomer at C_2 and C_3 is estimated to be nearly 180°, whereas that of the *cis* isomer is nearly 60°.

Compound **15** was obtained as a single isomer. The large coupling contant (J=8.8 Hz) at δ 2.70 and 4.45 in its ^{1}H-NMR spectrum is regarded as that of a *trans* isomer, in the same way as inferred for **12a′**.

Experimental

All melting and boiling points are uncorrected. IR spectra were taken on a Hitachi EPI-G2 spectrometer. ^{1}H-

NMR and ^{13}C-NMR spectra were recorded on a JEOL JNM-FX90Q spectrometer; all chemical shifts are given in ppm downfield from tetramethylsilane. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad.

Preparation of Substrates for Cyclization——Spectral and analytical data for all substrates used are listed in Tables III and IV. Among them, **1**, **2**, and **3** were prepared according to previously reported methods.[3] The other previously unknown compound were prepared as follows.

Preparation of **4**, **5** and **6**: Methylaminomethyl benzyl and propyl sulfide hydrochlorides (**16a**, **b**) were prepared from the corresponding primary amine hydrochloride, alkanethiol and formaldehyde, according to the previously reported method.[4] The previously unknown compound **16b**: mp 104—105 °C (CH_3CN). *N*-Ethoxycarbonylation of **16a** and **16b** by allowing them to react with ethyl chloroformate and triethylamine gave **4** and (*N*-methyl ethoxycarbamoyl)methyl propyl sulfide (**17**). Compound **17**: oil, IR ν_{max}^{neat} cm^{-1}: 1710 (C=O), ^{1}H-NMR (in $CDCl_3$) δ: 0.96 (3H, t, J=7.0 Hz, $CH_2CH_2C\underline{H}_3$), 1.23 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 1.15—1.85 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.49 (2H, t, J=7.5 Hz, $CH_2C\underline{H}_2S$), 2.86 (3H, s, NCH_3), 4.10 (2H, q, J=7.0 Hz, CH_2O), 4.38 (2H, s, NCH_2S). Oxidation of **4** and **17** with potassium permanganate in acetic acid gave **5** and **6**.

Preparation of **7a**—**c**: Aminoethyl benzyl sulfide (**18**) obtained by benzylation of aminoethanethiol was allowed to react with benzaldehyde and benzyl chloroformate in the usual manner to give **7a** and **7b**, respectively. For the preparation of **7c**, **18** was successively *N*-methylated (*N*-formylation followed by reduction with lithium aluminum hydride), *N*-ethoxycarbonylated and oxidized with potassium permanganate, by the usual methods.

Preparation of **10a**—**c** and **11a**, **b**: *o*-Benzylthio-, *o*-butylthio- and *o*-trimethylsilylmethylthioanilines (**19**,[5] **20**,[6] **21**) were prepared by alkylation of *o*-aminothiophenol. The new compound **21**: oil, IR ν_{max}^{neat} cm^{-1}: 3460, 3360 (NH), ^{1}H-NMR (in $CDCl_3$) δ: 0.16 (9H, s, $Si(CH_3)_3$), 2.05 (3H, s, NCH_3), 2.85 (2H, s, $SiCH_2N$), 6.5—7.4 (4H, m, C_6H_4). Usual condensation of **19** and **21** with benzaldehyde gave **10a** and **14**, respectively. *N*-Formylation of **19** and **20** followed by lithium aluminum hydride reduction gave the corresponding *N*-methyl derivatives (**22**, **23**).[7] Compound **22**: bp 147—148 °C (5 Torr), IR ν_{max}^{neat} cm^{-1}: 3380 (NH), ^{1}H-NMR (in $CDCl_3$) δ: 0.16 (9H, s, $Si(CH_3)_3$), 2.05 (3H, s, NCH_3), 2.85 (2H, s, $SiCH_2N$), 4.5—5.0 (1H, br, NH), 6.2—7.45 (4H, m, C_6H_4). *N*-Phenylthiomethylation of **22** by reaction with thiophenol and formaldehyde gave **10c** and *N*-ethoxycarbonylation of **22** and **23** gave the corresponding *o*-benzylthio- and *o*-butylthio-*N*-ethoxycarbonyl-*N*-methylanilines (**10c**, **24**). Compound **24**: oil, IR ν_{max}^{neat} cm^{-1}: 1710 (C=O), ^{1}H-NMR (in $CDCl_3$) δ: 1.3—1.7 (10H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.38 (2H, t, J=7.5 Hz, SCH_2), 3.97 (2H, q, J=7.0 Hz, OCH_2), 6.95—7.28 (4H, m, C_6H_4). Oxidation of **10c** and **24** with *m*-chloroperbenzoic acid gave **11a** and **11b**, respectively.

Cyclization to Thiazolidines (8a—f) and Thiomorpholines (9a, b) (see Table I)——General Procedure: A solution of a substrate (**1**—**4**, **7**—**8**) (0.03 mol) in 50 ml of THF was added dropwise to a solution of LDA (prepared from 0.09 mol of diisopropylamine and a hexane solution of 0.09 molar eq of butyllithium in 250 ml of THF) with stirring at −70 °C. The solution was stirred under the conditions shown in Table I. The reaction was quenched by addition of water (0.5 ml) and then carbon dioxide was passed through the solution. After concentration under reduced pressure, benzene was added to the resulting residue. Insoluble materials were filtered off. The filtrate was washed with water and dried over $MgSO_4$. The products **8a** and **8b** were obtained as their hydrochlorides by passing dry hydrogen chloride into the benzene solutions. The products **8c**, **d** and **9a**, **b** were obtained by distillation of the residue after removal of benzene.

In the case of entries **5** and **6**, the reaction was carried out under the conditions shown in Table I using 0.09 molar eq of NaH as a suspention.

Yields of the products are shown in Table I and their spectral and analytical data are listed in Table V.

The product **8b** [hydrochloride: mp 125—126 °C (EtOH), *Anal.* Calcd for $C_{17}H_{20}ClNS_2$: C, 60.42; H, 5.97; N, 4.14. Found: C, 60.26; H, 5.93; N, 4.45.] was easily converted by treatment with alkali to **8b′**, the data for which are listed in Table V.

Cyclization to Dihydro-1,4-benzothiazines (12a—c, 13a, b and 15) (see Table II)——General Procedure: A solution of a substrate (**10a**—**c**, **11a**, **b** and **14**) (0.01 mol) in 20 ml of THF was added dropwise to a solution of 0.03 molar eq of LDA in 80 ml of THF at −70 °C or to a suspension of 0.03 molar eq of NaH in 80 ml of THF at room temperature. The reaction was carried out under the conditions shown in Table II. After addition of saturated aqueous ammonium chloride, the THF layer was separated and the aqueous layer was extracted with benzene. The combined organic layer was dried over $MgSO_4$. After removal of the solvent, the residual solid was recrystallized from an appropriate solvent.

Yields of the products are listed in Table II and their spectral and analytical data are shown in Table IV.

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References and Notes

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