Highly Stereoselective Synthesis of the Anti-Platelet Activating Factor, 4-Thiazolidinones, Using Silyl Derivatives of 2-Mercaptoalkanoic Acids

Yoo Tanabe,* Hitomi Okumura, Masaki Nagaosa, and Masanari Murakami

School of Science, Kwansei Gakuin University, 1-1-155 Uegahara, Nishinomiya 662

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The cyclo-condensation of silyl 2-mercaptoalkanoates and arylmethyleneamines proceeded with high stereoselectivity to give alternatively both the *cis*- and *trans*-2,5-disubstituted 4-thiazolidinones, some of which are known as anti-platelet activating factor-active drugs. The use of the piperidine catalyst and no catalyst showed very high *cis*-stereoselectivity (*cis*/*trans*=10/1—50/1) during the reaction. On the other hand, the *trans*-selective reaction was promoted by Ti(O-*i*-Bu)$_4$ and Al(O-*s*-Bu)$_3$ catalysts (*cis*/*trans*=1/8—1/25). Both reactions were conducted with higher *cis*- and *trans*-selectivities as compared with those of the alkyl 2-mercaptoalkanoates under mild conditions. The cyclo-condensation using trimethylsilyl 2-(trimethylsilylthio)propionate and methyl 2-(trialkylsilylthio)propionates proceeded by the action of a catalytic amount (0.02 molar amount) of tetrabutylammonium fluoride with moderate *cis*-selectivity.

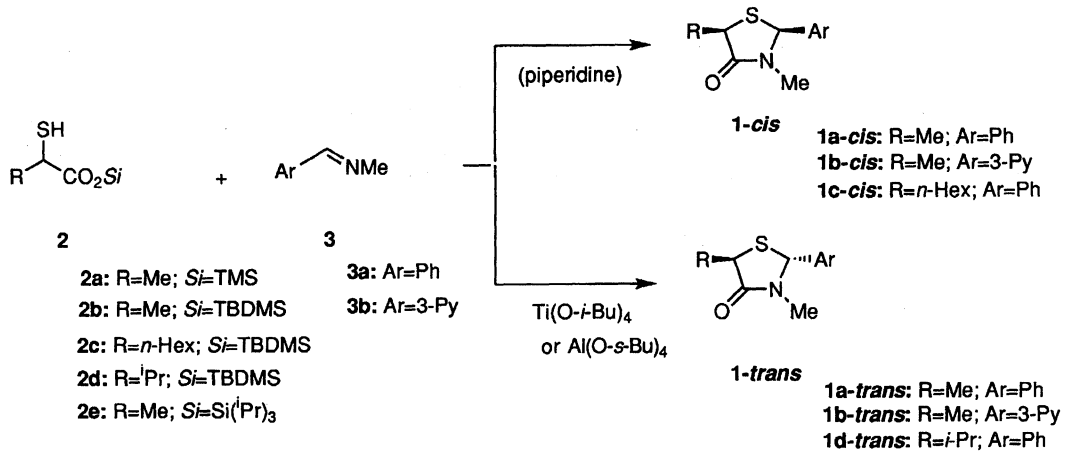
4-Thiazolidinones are recognized as worthwhile fundamental heterocyclic compounds,[1] comprising, for example, an anti-PAF (Platelet Activating Factor) drug in itself,[2] a key intermediate of β-lactam,[3] a sulfur containing mimic of D-ribose,[4] and oxygenase inhibitors.[5]

The syntheses of 2-aryl-4-thiazolidinones (**1**) were generally conducted by the condensation of 2-mercaptoalkanoic acids with primary amines and aromatic aldehydes (ArCHO) or with the corresponding Schiff bases.[6] However, there was little knowledge concerning the reaction conditions and the *cis*/*trans* stereoselectivity. Our previous papers described studies on an alternative method for the moderate stereoselective synthesis of these compounds[7] using alkyl 2-mercaptoalkanoates and arylmethyleneamines **3** (*cis*/*trans*=7/1—1/4 in the case of an important analog of **1**; R=Me) and its application to the structure-activity relationship of the anti-PAF 4-thiazolidinones.[2]

However, a more stereoselective method is desired for both the practical preparation of *cis*- or *trans*-**1** and screening of these analogs. The [3+2] stereocontrolled-type cyclo-condensation is still considered to be the most rational method for this stereoselective synthesis of **1**. We report here on a highly stereoselective synthesis of 4-thiazolidinones **1** using trimethylsilyl (TMS) or *t*-butyldimethylsilyl (TBDMS) 2-mercaptoalkanoate **2**, wherein both the *cis*- and *trans*-stereoselectivity are markedly enhanced compared with the reaction using the alkyl esters. Other silyl derivatives, i.e., trimethylsilyl 2-(trimethylsilylthio)propionate (**4**) and methyl 2-(trialkylsilylthio)propionates **5**, also underwent cyclo-condensation promoted not by the aforementioned piperidine or Ti(O-*i*-Bu)$_4$ catalyst, but by the catalytic use of tetrabutylammonium fluoride (TBAF) (0.02 molar amount). The selectivity was moderately *cis*-major.

Results and Discussion

Due to the higher reactivity of 2-mercaptoalkanoic acids compared with the corresponding alkyl esters during this cyclo-condensation,[7] the isosterism of 2-mercaptoalkanoic acids to the silyl 2-mercaptoalkanoates would be naturally promising. We first examined the reaction of trimethylsilyl (TMS) 2-mercaptopropionate (**2a**) with *N*-(benzylidene)methylamine (**3a**). The cyclo-condensation proceeded smoothyl at room temp in 76% yield with the elimination of trimethylsilanol (or hexamethyldisiloxane). This result was similar to that in the case of 2-mercaptoalkanoic acids. It is worth noting that the reaction of silyl ester **2a** showed higher stereoselectivity (*cis*/*trans*=15/1) than the mercaptoalkanoic acids and esters. In the case of the *t*-butyldimethylsilyl (TBDMS) ester **2b**, the *cis*/*trans* ratio decreased (*cis*/*trans*=10/1); however, the addition of piperidine (one molar amount) caused a significant enhancement in the *cis* ratio (*cis*/*trans*=50/1). Consequently, more highly *cis*-selective cyclocondensation effectively proceeded using no catalyst or catalytic piperidine compared with the reported method[7] using methyl 2-mercaptopropionate (the *cis*/*trans* ratio was at most 7/1). The piperidine catalyst affects the stereoselectivity rather than promotion of the reaction in the present case. This result was slightly different from that in the case of using methyl 2-mercaptopropionate. These results are summarized in Scheme 1 and Table 1.



Scheme 1.

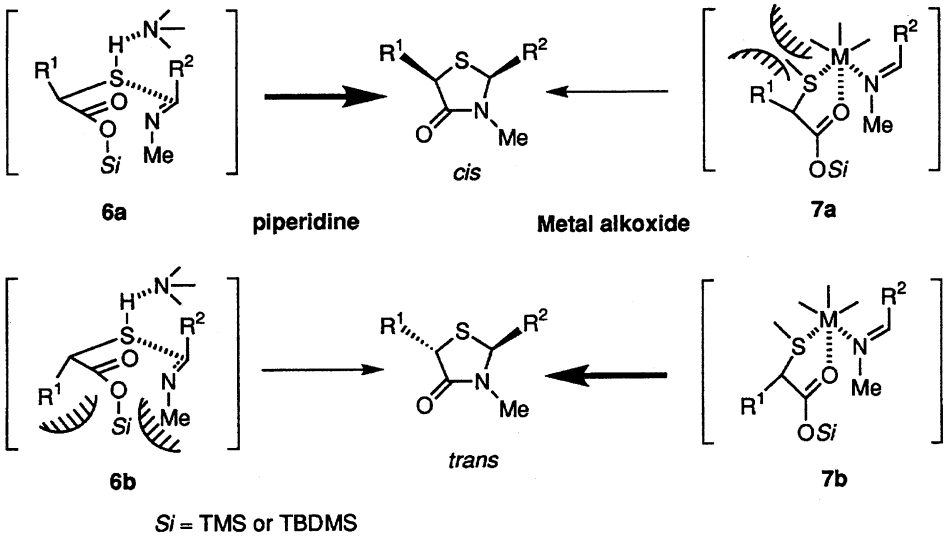
Table 1. Stereoselective Cyclo-condensation of Silyl 2-Mercaptoalkanoates **2** with Arylmethyleneamines **3**[a)]

Entry	Silyl ester **2** R	Silyl ester **2** *Si*	Arylmethyleneamines[b)]	Catalyst	Solvent	Temp °C	Product **1** *cis*/*trans*[c)]	Product **1** Yield%
1	Me	TMS	**3a**	None	Benzene	R.T.	15/1	76
2	Me	TBDMS	**3a**	None	Benzene	R.T.	10/1	82
3	Me	TBDMS	**3a**	Piperidine	Benzene	R.T.	50/1	51
4	Hex	TBDMS	**3a**	Piperidine	Benzene	R.T.	50/1	45
5	Me	TMS	**3b**	None	Benzene	−20	10/1	53
6	Me	TBDMS	**3b**	Piperidine	Benzene	0	10/1	64
7	Me	TBDMS	**3a**	Ti(O-*i*-Pr)$_4$	Benzene	R.T.	1/5	73
8	Me	TBDMS	**3a**	Ti(O-*i*-Bu)$_4$	Benzene	R.T.	1/15	82
9	Me	TBDMS	**3a**	Al(O-*s*-Bu)$_3$	Benzene	R.T.	1/15	46
10	^{i}Pr	TBDMS	**3a**	Ti(O-*i*-Bu)$_4$	Benzene	R.T.	1/25	58
11	Me	TBDMS	**3b**	Ti(O-*i*-Pr)$_4$	Benzene	R.T.	1/2	72
12	Me	TBDMS	**3b**	Ti(O-*i*-Bu)$_4$	Benzene	R.T.	—	Trace
13	Me	TMS	**3b**	Al(O-*s*-Bu)$_3$	CH_2Cl_2	−20	1/2	47
14	Me	TBDMS	**3b**	Al(O-*s*-Bu)$_3$	CH_2Cl_2	−20	1/8	64
15	Me	TIPS[d)]	**3a**	Piperidine	Benzene	R.T.	—	Trace
16	Me	TIPS[d)]	**3a**	Ti(O-*i*-Bu)$_4$	Benzene	R.T.	—	Trace

a) The reactions were carried out at R.T. for 10 h. Molar ratio is **2** : **3** : catalyst=1 : 1 : 1. b) **3a**: Ar=Ph, and **3b**: Ar=3-Pyridyl. c) Determined by ^{1}H NMR (400 MHz) analysis of *N*-methyl protons. d) Triisopropylsilyl.

On the other hand, metal alkoxides were expected to mediate the *trans*-cyclocondensation, since the chelation effect was observed in the case of alkyl esters.[7)] Thus, Ti(O-*i*-Pr)$_4$ or Ti(O-*i*-Bu)$_4$, an Al(O-*s*-Bu)$_3$ catalysts effectively promoted the *trans*-selective reaction of **2** under mild conditions, whereas other metal alkoxides, such as B(OMe)$_3$ and Zr(O-*i*-Pr)$_4$, or $(CF_3SO_3)_2Sn$, had little efficacy. Although the tendency of the catalysts basically agreed with the results of the previous method, the *trans*-selectivity was superior to that in the case using alkyl esters. Of note is that the nature of the metal alkoxide catalysts and arylmethyleneamines **3** significantly influenced the reaction: (1) Ti(O-*i*-Bu)$_4$ and Al(O-*s*-Bu)$_3$ exhibited distinctive *trans*-selectivity; (2) Ti(O-*i*-Pr)$_4$ was inferior to Ti(O-*i*-Bu)$_4$, whose results were in contrast to the previous method using 2-mercaptoalkanoic esters; (3) Ti(O-*i*-Bu)$_4$ matched with benzylideneamine **3a** and Al(O-*s*-Bu)$_3$ with 3-pyridylmethyleneamine **3b**; and (4) the TBDMS esters **2b—d** were more effective than the TMS ester **2a** with respect to stereoselectivity.

The use of a nonpolar solvent (benzene or CH_2Cl_2) was suitable (Table 1). Bulkyl triisopropylsilyl (TIPS) ester **2e** was unreactive for the cyclo-condensation. The reaction mechanism is considered to be similar to that of 2-mercaptoalkanoic esters,[7)] wherein the bulky silyl group would distinctively contribute to the enhancement of the alternative stereoselectivities, as shown in Scheme 2. In the case of a piperidine-catalyzed reaction, a steric repulsion between the R^1 substituent, the trialkylsilyl group, and the *N*-methyl group, of transition states **6b**, compared with **6a**, would more preferentially lead to *cis*-4-thiazolidinones. On the contrary, in the case of a metal-catalyzed reaction, Ti and Al alkoxides would coordinate sulfur, nitrogen, and/or carbonyl oxygen to form packed transition states **7a** or **7b**. Due



Scheme 2.

to a steric hindrance between alkoxy ligands and the R^1 substituent, *trans*-4-thiazolidinones are predominantly given from transition states **7b**.

We next tested trimethylsilyl 2-(trimethylsilylthio)-propionate (**4**) based on the aforementioned results, expecting that the reactivity of the cyclocondensation would be enhanced. However, the reactions of silyl substrate **4** with benzylideneamine **3a** using piperidine and Ti(O-*i*-Bu)$_4$ catalysts in benzene resulted in lower yields of 4-thiazolidinone **1a** (trace and 32%, respectively). A catalytic use of TMS trifluoromethanesulfonate (0.05 molar amount) in this reaction (CH_2Cl_2, −78—0 °C) gave the desired product **1a** in only 10% yields, although a high *cis*-selectivity (*cis*/*trans*=8/1) was shown; the hydrolysis of benzylideneamine **3a** giving benzaldehyde mainly proceeded.

Meanwhile, the fluoride ion is well recognized to activate the silicon–heteroatom bond.[8] Recently, we reported that catalytic tetrabutylammonium fluoride (TBAF) promoted mild and effective silyl transfer reactions from nitrogen,[9] hydrogen, and silicon[10] toward the hydroxyl group. In addition, we are now studying an epoxy-ring opening with thiosilanes catalyzed by TBAF.[11] Along with these investigations, the TBAF catalyst (0.02 molar amount) was applied to the cyclocondensation using **4** and methyl 2-(trimethylsilylthio)propionate (**5a**). Thus, these substrates, **4** and **5a**, underwent the desired reaction effectively catalyzed by TBAF. It is notable that these reactions did not proceed without the TBAF catalyst using benzene and THF solvents, except in the case of using DMF. However, the stereoselectivity of the reaction was low (*cis*/*trans*=1.5/1—3/1) compared with the aforementioned piperidine, Ti(O-*i*-Bu)$_4$, and Al(O-*s*-Bu)$_3$, catalyzed reaction. The TBDMS analog **5b** underwent the reaction in a poor yield (25% at best in benzene). These results are shown in Scheme 3 and Table 2.

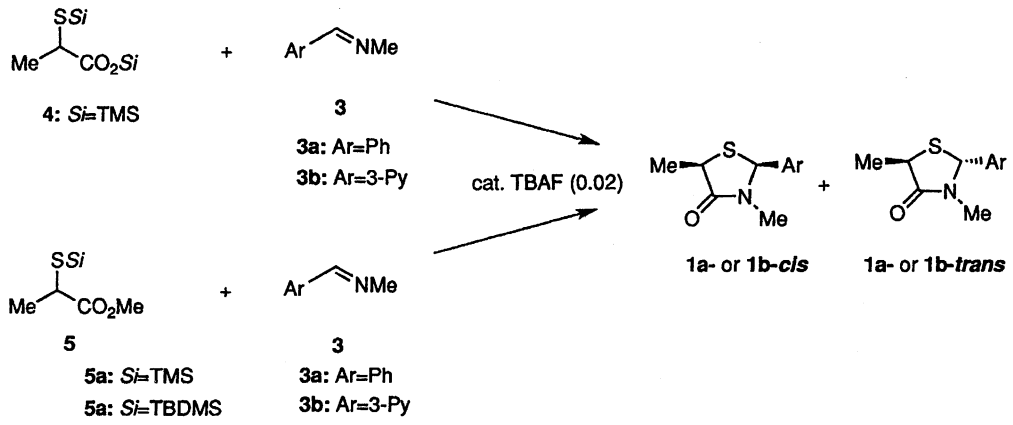
In conclusion, several silyl derivatives, **2**, **4**, and **5**, effectively underwent [3+2] cyclo-condensations, and silyl ester **2** especially served as a substrate for a highly stereoselective (both *cis* and *trans*) reaction. Employing the present method, the syntheses of several optically active analogs are now in progress. Their structure–anti-PAF activity relationships will be reported in the future.

Experimental

Apparatus and Materials. The boiling points were uncorrected. ^{1}H NMR spectra were recorded on a JEOL EX-90 (90 MHz) or a JEOL α (400 MHz) spectrometer using TMS as an internal standard in $CDCl_3$. IR spectra were recorded on a Hitachi 270-30 spectrophotometer. MS spectra were obtained with a Hitachi GC/MS M-80 instrument. The reagents were of commercial grade and were use without further purification. Silica-gel column chromatography was performed on a Merck Art. 7734 or 9385.

Trimethylsilyl 2-Mercaptopropionate (2a). A mixture of 2-mercaptopropionic acid (3.18 g, 30 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (4.84 g, 30 mmol) in 1,2-dichloromethane (45 ml) was refluxed for 2 h. After cooling the mixture, evaporation and distillation of the residue gave 3.32 g (62%) of **2a**. Colorless liquid; bp 62—65 °C/13 mmHg (1 mmHg=133.3 Pa); IR (film) 2970, 1725, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.30 (9H, s), 1.50 (3H, d, J=7.0 Hz), 2.10 (1H, d, J=9.0 Hz), 3.25—3.65 (1H, m). Found: C, 40.76; H, 7.93%. Calcd for $C_6H_{14}O_2SSi$: C, 40.41; H, 7.91%.

***t*-Butyldimethylsilyl 2-Mercaptopropionate (2b).** To a stirred solution of 2-mercaptopropionic acid (3.00 g, 28.3 mmol) and triethylamine (3.15 g, 31.2 mmol) in DMF (50 ml) was added *t*-butylchlorodimethylsilane (4.70 g, 31.2 mmol) with sufficient stirring at R.T. The mixture was stirred for 15 h at R.T., and then poured onto ice-water and extracted with ether. The organic phase was washed with water, brine, dried (Na_2SO_4), concentrated, and distilled to give 3.56 g (57%) of **2b**. Colorless liquid; bp 98—100 °C/18 mmHg; IR (film) 2820, 1720, and 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.30 (6H, s), 0.60 (9H, s), 1.50 (3H,



Scheme 3.

Table 2. Catalytic TBAF Promoted Cyclo-condensation Using Silyl Derivatives **4** and **5** with Arylmethyleneamines **3**[a)]

Entry	Substrate	S-	O-	Arylmethylene-amine[b)]	Solvent	Temp °C	Product **1** *cis/trans*[c)]	Yield/%[d)]
1	**4**	TMS	TMS	**3a**	CH_2Cl_2	0	2/1	67 (trance)
2	**4**	TMS	TMS	**3a**	THF	R.T.	1.5/1	60 (trance)
3	**4**	TMS	TMS	**3a**	DMF	R.T.	2/1	43 (38)
4	**5a**	TMS	Me	**3a**	CH_2Cl_2	R.T.	1.5/1	36 (trance)
5	**5a**	TMS	Me	**3a**	THF	R.T.	3/1	46 (trance)
6	**5a**	TMS	Me	**3b**	THF	R.T.	1/1	46 (trance)
7	**5b**	TBDMS	Me	**3a**	Benzene	R.T.	3/1	25 (trance)

a) The reactions were carried out at R.T. for 10 h. Molar ratio is **4**(or **5**) : **3** : catalyst=1 : 1 : 0.02. b) **3a**: Ar=Ph, and **3b**: Ar=3-Pyridyl. c) Determined by ^{1}H NMR (90 MHz) analysis of *N*-methyl protons. d) Parentheses mean the yields *without* TBAF catalyst.

d, J=7.0 Hz), 2.10 (1H, d, J=9.0 Hz), 3.25—3.70 (1H, m). Found: C, 49.39; H, 8.98%. Calcd for $C_9H_{20}O_2SSi$: C, 49.04; H, 9.15%.

***t*-Butyldimethylsilyl 2-Mercaptooctanoate (2c).** Similar to the procedure for preparing **2b** using 2-mercaptooctanonic acid, **2c** was obtained in 44% yield. Colorless liquid; by 150 °C (oven temp)/0.9 mmHg (bulb to bulb distillation); IR (film) 2820, 1720, and 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.30 (6H, s), 0.90 (9H, s), 0.60—1.50 (13H, m), 2.00 (1H, d, J=9.0 Hz), 3.20—3.50 (1H, m). Found: C, 58.14; H, 10.15%. Calcd for $C_{14}H_{30}O_2SSi$: C, 57.87; H, 10.41%.

***t*-Butyldimethylsilyl 2-Mercapto-3-methylbutanoate (2d).** Similar to the procedure for preparing **2b** using 2-mercapto-3-methylbutanoic acid, **2d** was obtained in 55% yield. Colorless liquid; bp 120 °C (oven temp)/1.0 mmHg (bulb to bulb distillation); IR (film) 2820, 1720, and 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.30 (6H, s), 0.60 (9H, s), 1.05 (3H, d, J=6.0 Hz), 1.15 (3H, d, J=6.0 Hz), 1.95—2.30 (1H, m), 2.10 (1H, d, J=9.0 Hz), 3.15 (1H, dd, J=9.0 and 9.0 Hz). Found: C, 53.33; H, 9.53%. Calcd for $C_{11}H_{24}O_2SSi$: C, 53.17: H, 9.74%.

Triisopropylsilyl 2-Mercaptopropionate (2e). Similar to the procedure for preparing **2b**, a reaction using chloro(triisopropyl)silane in the place of *t*-butylchlorodimethylsilane gave **2e** in 67% yield. Colorless liquid; bp 100—102 °C/2.0 mmHg; IR (film) 2950, 1720, 1275, and 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.00—1.60 (24H, m), 2.10 (1H, d, J=9.0 Hz), 3.25—3.75 (1H, m). Found: C, 55.18; H, 9.72%. Calcd for $C_{12}H_{26}O_2SSi$: C, 54.91; H, 9.98%.

Trimethylsilyl 2-(Trimethylsilylthio)propionate (4). A mixture of 2-mercaptopropionic acid (1.00 g, 9.4 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (3.80 g, 23 mmol) was refluxed for 10 h. After cooling the mixture, evaporation and distillation of the residue gave 1.48 g (59%) of **4**. Colorless liquid; bp 101—103 °C/35 mmHg; IR (film) 2960, 1720, 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.30 (9H, s), 0.35 (9H, s), 1.45 (3H, d, J=7.0 Hz), 3.35 (1H, q, J=7.0 Hz). Found: C, 42.88; H, 8.70%. Calcd for $C_9H_{22}O_2SSi_2$: C, 43.15; H, 8.85%.

Methyl 2-(Trimethylsilylthio)propionate (5a). A mixture of methyl 2-mercaptopropionate (4.90 g, 40.7 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (13.3 g, 81.6 mmol) was refluxed for 10 h. After cooling the mixture, evaporation and distillation of the residue gave 16.0 g (83%) of **5a**. Colorless liquid; bp 100—102 °C/60 mmHg; IR (film) 2980, 1755, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.35 (9H, s), 1.50 (3H, d, J=7.0 Hz), 3.45 (1H, q, J=7.0 Hz), 3.78 (3H, s). Found: C, 43.84; H, 8.31%. Calcd for $C_7H_{16}O_2SSi$: C, 43.71; H, 8.38%.

Methyl 2-(*t*-Butyldimethylsilylthio)propionate (5b). To a stirred solution of methyl 2-mercaptopropionate (3.60 g, 30.0 mmol) and DBU (4.10 g, 27.0 mmol) in benzene (60 ml) was added *t*-butylchlorodimethylsilane (4.06 g, 27.0 mmol) in benzene (20 ml) with stirring at 5—10 °C. After the mixture had been stirred for one hour at R.T. it was filtered with Celite, concentrated, and distilled to give 0.82 g (35%) of **5b**. Colorless liquid; bp 65—67 °C/40 mmHg;

IR (film) 2960, 2940, 1750, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.10 (6H, s), 0.90 (9H, s), 1.55 (3H, d, J=7.0 Hz), 3.50 (1H, q, J=7.0 Hz), 3.75 (3H, s). Found: C, 51.40; H, 9.66%. Calcd for $C_{10}H_{22}O_2SSi$: C, 51.23; H, 9.46%.

***N*-(Benzylidene)methylamine (3a).** Colorless liquid; bp 69—72 °C/18 mmHg (lit,[12] 185 °C/18 mmHg); IR (film) 2850, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.50 (3H, d, J=1.5 Hz), 7.30—7.50 (3H, m), 7.55—7.80 (2H, m), 8.25 (1H, d, J=1.5 Hz).

***N*-(3-Pyridylmethylene)methylamine (3b).** To a stirred aqueous solution of methylamine (40%; 100 ml) was added nicotinaldehyde (3-pyridinecarbaldehyde) (10.7 g, 0.10 mol) at R.T., which was stirred for an hour. Water and methylamine were then evaporated under reduced pressure from the mixture and the residue was distilled to give 10.5 g (88%) of **3b**. Pale-yellow liquid; bp 102—103 °C/20 mmHg; IR (film) 2850, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.55 (3H, d, J=2.0 Hz), 7.20—8.90 (5H, m). Found: C, 69.77; H, 6.59; N, 23.05%. Calcd for $C_7H_8N_2$: C, 69.97; H, 6.71; N, 23.32%.

A Typical Procedure of Highly *cis*-Predominant Cyclo-condensation: To a stirred solution of *t*-butyldimethylsilyl 2-mercaptopropionate (**2b**; 220 mg, 1.0 mmol) in benzene (2.0 ml) was added successively piperidine (85 mg, 1.0 mmol) and *N*-(benzilidene)methylamine (**3a**; 119 mg, 1.0 mmol) at R.T. with stirring and allowed to stand at R.T. for 10 h. After water had been added to the mixture, it was extracted with ethyl acetate and washed with water, brine, dried (Na_2SO_4), and concentrated. The crude oil obtained was purified by silica-gel column chromatography (hexane/ethyl acetate=3 : 1) to give 3,5-dimethyl-2-phenylthiazolidin-4-one (**1a-*cis***; 105 mg, *cis*/*trans*=50/1 determined by integration of the 3-methyl protons of ^1H NMR[7]) in 51% yield. Determination of *cis* or *trans* structure was by ^1H NMR[3] and X-ray crystallographic analyses.[7] Colorless liquid; IR (film) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.65 (3H, d, J=7.0 Hz), 2.65 (3H, d, J=2.0 Hz), 3.90 (1H, q, J=7.0 Hz), 5.45 (1H, s), 7.20—7.50 (5H, m). Found: C, 63.45; H, 6.22; N, 6.67%. Calcd for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76%.

A Typical Procedure of Highly *trans*-Predominant Cyclo-condensation: To a stirred solution of *t*-butyldimethylsilyl 2-mercaptopropionate (**2b**; 110 mg, 0.5 mmol) in benzene (2.0 ml) was added successively titanium (IV) isobutoxide (170 mg, 0.5 mmol) and *N*-(benzylidene)methylamine (**3a**; 54 mg, 0.5 mmol) at R.T. with stirring, and allowed to stand at R.T. for 10 h. Water was then added to the mixture, and, after Celite filtration, it was extracted with ethyl acetate and the organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The crude oil obtained was purified by silica-gel column chromatography (hexane/ethyl acetate=3 : 1) to give 3,5-dimethyl-2-phenylthiazolidin-4-one (**1a-*trans***; 85 mg, *cis*/*trans*=1/15, determined by ^1H NMR) in 82% yield. Colorless liquid; IR (film) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.60 (3H, d, J=7.0 Hz), 2.70 (3H, s), 3.90—4.20 (1H, m), 5.45 (1H, d, J=2.0 Hz), 7.20—7.40 (5H, m).

A Typical Procedure of Catalytic TBAF Promoted Cyclo-condensation: To a stirred solution of **4** (250 mg, 1.0 mmol) in CH_2Cl_2 (2.0 ml) was added successively TBAF (1 M-THF solution, 20 µl) and *N*-(benzylidene)methylamine (**3a**; 119 mg, 1.0 mmol) at R.T. with stirring and allowed to stand at R.T. for 10 h. Water was added to the mixture, which was extracted with CH_2Cl_2; the organic phase was then washed with water, brine, dried (Na_2SO_4), and concentrated. The crude oil obtained was purified by silica-gel column chromatography (hexane/ethyl acetate=3 : 1) to give 3,5-dimethyl-2-phenylthiazolidin-4-one (**1a**; 139 mg, *cis*/*trans*=2/1, determined by ^1H NMR) in 67% yield.

***cis*-3,5-Dimethyl-2-(3-pyridyl)thiazolidin-4-one (1b-*cis*).** Colorless crystals, mp 95—98 °C (lit,[7b] 98—99 °C); IR (film) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.65 (3H, d, J=7 Hz), 2.70 (3H, s), 3.95 (1H, q, J=7 Hz), 5.50 (1H, s), 7.20—7.80 (2H, m), 8.40—8.70 (2H, m).

***trans*-3,5-Dimethyl-2-(3-pyridyl)thiazolidin-4-one (1b-*trans*).** Colorless crystals, mp 80—81 °C (lit,[7b] 80—82 °C); IR (film) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.60 (3H, d, J=7 Hz), 2.75 (3H, d, J=2 Hz), 3.80—4.10 (1H, m), 5.50 (1H, d, J=2 Hz), 7.20—7.75 (2H, m), 8.40—8.70 (2H, m).

***cis*-5-Hexyl-3-methyl-2-phenylthiazolidin-4-one (1c-*cis*).** Colorless liquid; IR (film) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.85 (3H, t, J=7 Hz), 1.20—1.70 (10H, m), 2.70 (3H, s), 3.90 (1H, dd, J=10 and 2 Hz), 5.45 (1H, s), 7.20—7.50 (5H, m). Found: C, 69.10; H, 8.13; N, 4.93%. Calcd for $C_{16}H_{23}NOS$: C, 69.27; H, 8.36; N, 5.05%.

***trans*-5-Isopropyl-3-methyl-2-phenylthiazolidin-4-one (1d-*trans*).** Colorless liquid; IR (film) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.05 (3H, d, J=7 Hz), 1.25 (3H, d, J=7 Hz), 2.40—2.70 (1H, m), 2.70 (3H, s), 4.00—4.20 (1H, m), 5.40 (1H, d, J=2 Hz), 7.00—7.40 (5H, m). Found: C, 66.12; H, 7.19; N, 5.89%. Calcd for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28; N, 5.95%.

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