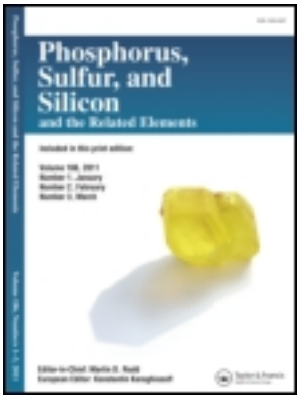

Phosphorus, Sulfur, and Silicon and the Related Elements

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A Convenient Synthesis of Thiazolidin-2-ones from Thiazolidine-2-thiones: Antibiotic Activity and Revisiting the Mechanism

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A CONVENIENT SYNTHESIS OF THIAZOLIDIN-2-ONES FROM THIAZOLIDINE-2-THIONES: ANTIBIOTIC ACTIVITY AND REVISITING THE MECHANISM

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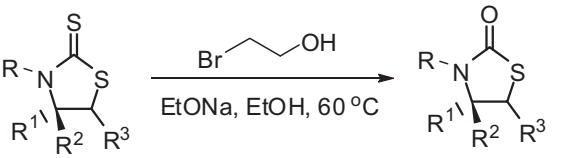
GRAPHICAL ABSTRACT



Abstract *Various substituted thiazolidin-2-ones were synthesized from the corresponding thiazolidine-2-thiones with bromoethanol in ethanol with sodium ethoxide as a base. The optimal reaction conditions and mechanism were reinvestigated in detail. The bioassay indicated that (S)-4-isobutyl and (S)-4-benzylthiazolidin-2-ones show certain inhibitive activities against Candida albicans and Escherichia coli.*

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Keywords Bromoethanol; mechanism; sodium ethoxide; thiazolidin-2-one; thiazolidine-2-thione

INTRODUCTION

Thiazolidin-2-ones (**1**) are important compounds in both pharmaceutical and synthetic organic chemistry. They have been widely used as building blocks in the synthesis of valuable natural products,[1] pesticides,[2] and other compounds with anti-HIV[3] and anticancer activities.[4] It is well known that the derivatives of thiazolidine-2-thione (**2**),[5] oxazolidine-2-thione (**3**),[6] and oxazolidin-2-one (**4**)[7] have been extensively applied as chiral auxiliaries in

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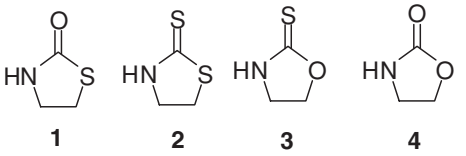
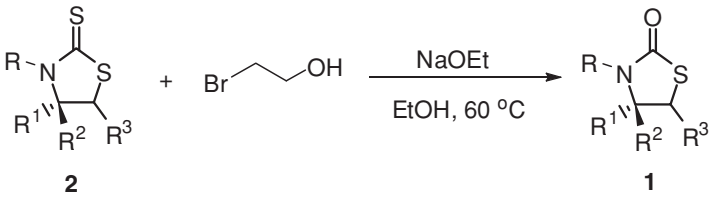


Figure 1 Thiazolidin-2-one (**1**), thiazolidine-2-thione (**2**), oxazolidine-2-thione (**3**), and oxazolidin-2-one (**4**).

numerous asymmetric syntheses (Figure 1). As their analogs, the derivatives of thiazolidin-2-one (**2**) will have broad applications in the field as well.

Several synthetic methods for thiazolidin-2-one and substituted thiazolidin-2-ones have been developed. Thiazolidin-2-ones have been synthesized via the ring-closing procedure of vicinal aminomercaptans with phosgene or triphosgene,[8] 1,1′-carbonyldiimidazole,[9] urea,[10] or carbon monoxide[11] under the catalysis of Se[11a,b] or S[11c] and ethyl carbonochloridate under the catalysis of hydrotalcites.[12] Desulfurization (the S/O-exchange) of thiazolidine-2-thiones is an alternative method for synthesizing the corresponding thiazolidin-2-ones via reactions with oxiranes[13] or hydrogen peroxide.[14] Other synthetic methods, including the ring-closing of aminoethanol or haloethylamine with carbonyl sulfide,[15] the O/S-exchange of oxazolidine-2-thione or oxazolidin-2-ones[16] and the cyclization of iodoalkyl thiocyanates,[17] were also reported in the literature.

Most of the reported preparative methods require harsh conditions (high temperature or pressure) or toxic reagents such as selenium or phosgene. Furthermore, for the ring-closing method, most vicinal aminomercaptans are not commercially available. Thiazolidine-2-thiones **2** can be prepared conveniently from commercially available amino alcohols and carbon disulfide in the presence of sodium hydroxide. Recently, Weng and coworkers converted thiazolidine-2-thione itself to thiazolidin-2-one with chloroethanol under basic conditions and noted that thiazolidin-2-one shows some antibacterial activity.[18] To search for new antibiotic agents, we hoped to prepare substituted thiazolidin-2-ones from easily synthesized thiazolidine-2-thiones via the S/O-exchange with haloethanols as reagents for bioassay. We herein present the synthesis of various thiazolidin-2-ones with further investigation into the reaction conditions and mechanism (Scheme 1).



Scheme 1 Synthesis of thiazolidin-2-ones from thiazolidine-2-thiones.

RESULTS AND DISCUSSION

First, we synthesized a series of thiazolidine-2-thiones and planned to convert them to the corresponding thiazolidin-2-ones according to the reported procedure: thiazolidine-2-thione, bromoethanol, and sodium ethoxide (1:1.4:1 in molar ratio) in ethanol were stirred at 60 °C for 4 h.[18] After finishing several examples, we found that thiazolidine-2-thione

Table 1 Optimizing reaction conditions for synthesis of thiazolidin-2-ones

Entry	Thiazolidine-2-thione	$R/R^1/R^2/R^3$	Reaction Conditions[a]	Product(s)	Yield (%)
1	**2a**	H/H/H/H	60 °C, 4 h, EtONa	**1a**	40
2	**2b**	H/Me/H/H	60 °C, 4 h, EtONa	**1b**	45
3	**2c**	H/Ph/H/H	60 °C, 4 h, EtONa	**1c**	75
4	**2c**	H/Ph/H/H	60 °C, 4 h, EtONa $ClCH_2CH_2OH$	**1c**	70
5	**2d**	H/*i*Pr/H/H	60 °C, 4 h, EtONa	**1d**	85
6	**2e**	H/*i*Bu/H/H	60 °C, 4 h, EtONa	**1e**	73
7	**2c**	H/Ph/H/H	60 °C, 1 h, EtONa	**1c & 5c**	81 (1:7)
8	**2e**	H/*i*Bu/H/H	60 °C, 1 h, EtONa	**1e & 5e**	81 (1:5)
9	**2e**	H/*i*Bu/H/H	80 °C, 1 h, EtONa	**1e**	67
10	**2e**	H/*i*Bu/H/H	60 °C, 1 h, 3 eq. EtONa	**1e**	70
11	**2e**	H/*i*Bu/H/H	60 °C, 4 h, NaOH	**1e**	38
12	**2e**	H/*i*Bu/H/H	60 °C, 4 h, K_2CO_3	**1e**	23
13	**2c**	H/Ph/H/H	RT, 1 h, EtONa	**5c**	80
14	**2e**	H/*i*Bu/H/H	RT, 1 h, EtONa	**5e**	82
15	**2l**	Bn/Bn/H/H	60 °C, 4 h, EtONa	No reaction	—

[a]With $BrCH_2CH_2OH$.

(**2a**) itself and its 4-methyl derivative (**2b**) gave rise to the corresponding 2-thiazolidinones in relatively low yields in comparison with other substituted thiazolidine-2-thiones, such as (*S*)-4-pheny-thiazolidine-2-thione (**2c**), (*S*)-4-isopropyl-thiazolidine-2-thione (**2d**), and (*S*)-4-isobutyl-2-thiazolidine-2-thione (**2e**) (Table 1, entries 1–5). The yield of product **1a** did not reach the reported value (80%). We had to reinvestigate the reaction conditions and the mechanism of the formation of thiazolidin-2-ones.

We initially selected the reaction of (*S*)-4-phenylthiazolidine-2-thione (**2c**) as a model reaction to optimize the reaction conditions, because both its starting material and product show obvious absorption under ultraviolet (UV) light for convenient thin-layer chromatography (TLC) analysis. When we traced the reaction process with TLC, we found that the reaction might have already completed in 1 h because the possible product **1c** ($R_f = 0.54$, PE: EA = 3:2, *v/v*) was generated and **2c** ($R_f = 0.77$, PE: EA = 3:2, *v/v*) disappeared. Furthermore, a byproduct (**5c′**, $R_f = 0.36$, PE: EA = 3:2, *v/v*) was also observed. Therefore, we stopped the reaction after 1 h and separated the major product (81% yield) and by-product (**5c′**, 3% yield) on a silica gel column. However, the ^{1}H-NMR spectrum of the major product revealed that it was a mixture of two compounds (the products **1c** and **5c** in a ratio of 1:7) that cannot be separated via column chromatography due to their close polarity (Table 1, entry 7). Thus, we had to try another substrate **2e** and hoped that its products were separable on TLC. We conducted the reaction with **2e** ($R_f = 0.50$, PE: EA = 4:1, *v/v*) under the same conditions, and TLC analysis demonstrated that another new product **5e** ($R_f = 0.40$, PE: EA = 4:1, *v/v*) as the major product was generated in the reaction at 1 h in addition to the desired product **1e** ($R_f = 0.33$, PE: EA = 4:1, *v/v*; Table 1, entry 8). Both **1e** and the new product **5e** were obtained after column chromatographic separation. ^{1}H- and ^{13}C-NMR spectra indicated that the new product **5e** had a more CH_2CH_2 group than substrate **2e**. In addition, a new absorption peak appeared at 166.9 ppm in ^{13}C-NMR with the disappearance of the thiocarbonyl group. The infrared (IR) spectrum confirmed

Table 2 Typical absorption in spectra of compounds **1**, **2**, **5**, and **5′**

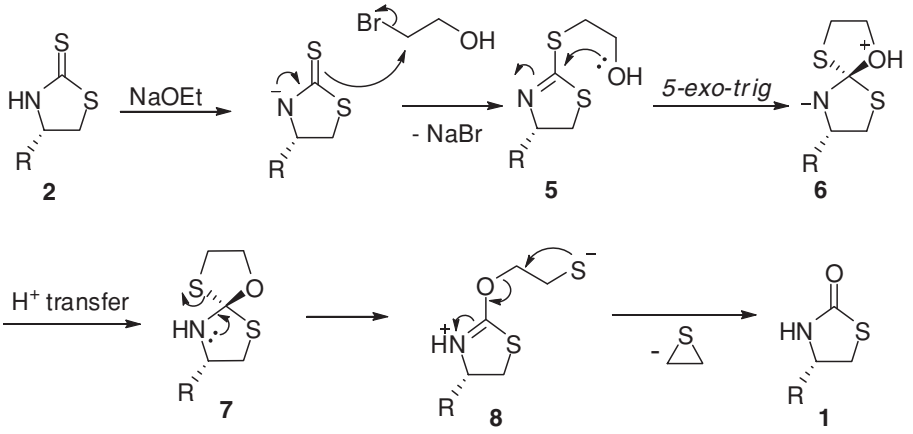
Entry	Compounds	^{13}C-NMR (ppm)	IR (cm^{-1})	^{1}H-NMR (ppm)
1	**1e**	175.7 (C=O)	1674 (C=O)	6.82 (NHC=O)
2	**2e**	200.5 (C=S)	1268 (C=S)	8.42 (NHC=S)
3	**5e**	166.9 (C=N)	1558 (C=N)	5.10 (OH)
4	**1c**	175.2 (C=O)	1674 (C=O)	6.21 (NHC=O)
5	**2c**	201.5 (C=S)	1267(C=S)	8.03 (NHC=S)
6	**5c**	169.0 (C=N)	1556 (C=N)	4.44 (OH)
7	**5c′**	198.3 (C=S)	1261 (C=S)	2.35 (OH)

that no carbonyl group formed, but there was a strong absorption at 1558 cm^{-1}. This validated that there must be a C=N bond in compound **5e**. Thus, it should be the *S*-alkylation product, (*S*)-2-hydroxyethylthio-4-isobutylthiazoline (**5e**), which was further verified by high-resolution mass spectrometry (HRMS) and elemental analysis. Some typical spectral data of compounds **1**, **2**, **5**, and **5′** are listed in Table 2.

After the structure of **5e** was identified, the mixed products in the reaction of **2c** were ascertained to be a mixture of (*S*)-4-phenylthiazolidin-2-one (**1c**) and (*S*)-2-hydroxyethylthio-4-phenylthiazoline (**5c**). We tried to purify **5c** via recrystallization. The mixture of **5c** and **1c** was dissolved in refluxing EtOH and a large amount of colorless crystals was crystallized as the temperature decreased. However, only **1c** was crystallized according to its nuclear magnetic resonance (NMR) spectra. Moreover, after removing the solvent of the filtrate, only a small amount of mixture remained. This demonstrated that compound **5c** was converted to the product **1c** in refluxing ethanol. To further confirm the conversion, pure **5e** was refluxed in EtOH, affording **1e** quantitatively after cooling. Subsequently, we found that **5e** can transform to **1e** slowly in EtOH at r.t. (for 2 days) as well.

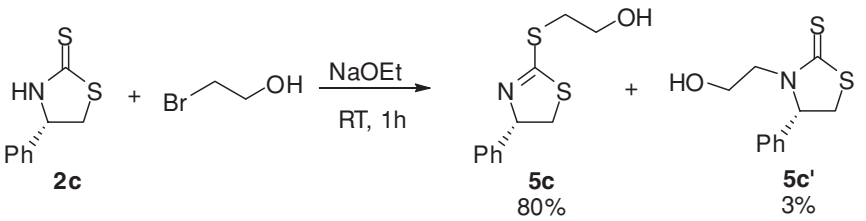
The less steric thiazolidin-2-ones **1a** and **1b** were crystallized from diethyl ether due to lower melting points. Some 2-(2-hydroxyethylthio)thiazolidines **5a** and **5b** did not convert to the corresponding products **1a** and **1b** in refluxing ether because its boiling point is obviously lower than that of ethanol, resulting in relatively lower yields. In the reported procedure, **1a** was purified by distillization at a high temperature, favorably transforming **5a** to **1a**. After prolonging the refluxing time and increasing the temperature of the reaction, the yields of **1a** and **1b** were improved obviously.

It was reported that thiazolidine-2-thiones react with alkyl halides in the presence of a base to produce the corresponding 2-alkylthiothiazolines.[19] On the basis of the formation mechanism of thiazolidin-2-ones from thiazolidine-2-thiones and oxirane,[13a] the conversion mechanism from thiazolidine-2-thiones to thiazolidin-2-ones was proposed as follows[18]: thiazolidine-2-thiones **2** were alkylated firstly on their *S*-atom with haloethanols to afford 2-(2-hydroxyethylthio)thiazolidines **5** in the presence of a base (NaOEt), which further underwent an intramolecular *5-exo-trig* ring-closing process to form zwitterionic intermediates **6**, followed by a proton transfer to give rise to the spiro intermediates **7**. Unstable intermediates **7** readily underwent a ring-opening reaction to generate new alkylthiothiazolidine intermediates **8**,[20] which subsequently released a molecule of thirane via an intramolecular nucleophilic substitution to afford thiazolidin-2-ones **1** (Scheme 2). In the process, 2-(2-hydroxyethylthio)thiazolidines **5** were the key intermediates to determine whether the reactions occurred or not. Subsequently, we explored whether intermediates **5**



Scheme 2 Mechanism for the generation of thiazolidin-2-ones.

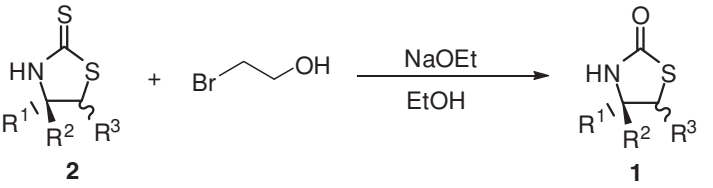
could be afforded under mild conditions. The reaction of **2c** with bromoethanol and NaOEt was conducted at r.t. for 1 h. No **1c** was formed and pure **5c** was obtained in an 80% yield via column chromatograph (entries 13–14, Table 1). In addition, by-product **5c′** was obtained in a 3% yield. ^{1}H-NMR and HRMS indicated that it was an isomer of **5c**. We hypothesized initially that it might be the spiro intermediate **7c**. Nevertheless, there was an absorption peak of the C=S group at 198.3 ppm in the ^{13}C-NMR spectrum, revealing that it is the *N*-alkylated product of **2c**: (*S*)-*N*-hydroxyethyl-4-phenylthiazolidine-2-thione (**5c′**) (Scheme 3). We obtained the intermediates **5** and verified the conversion from **5** to **1**. To further confirm the proposed mechanism, we used (*S*)-*4*,*N*-dibenzylthiazolidine-2-thione (**2l**) as the starting material to conduct the reaction. However, no new product was observed (Table 1, entry 15). This illustrated that if there was no H-atom on the N-atom, neither intermediate **5** nor the corresponding thiazolidin-2-one **1** yielded. However, if there was no substituent on the nitrogen atom, intermediate **5** was generated initially and then converted to the corresponding 2-thiazolidinone **1**. Our results provide the experimental evidence for the proposed conversion mechanism from thiazolidine-2-thiones to thiazolidin-2-ones via the reaction with haloethanols.



Scheme 3 *S*-Alkylation and *N*-alkylation of (*S*)-4-pheny-thiazolidine-2-thione (**2c**).

After understanding the reaction very well, further application was used for the preparation of 5-substituted, 4,4-disubstituted, and 4,5-disubstituted thiazolidine-2-ones. All of these reactions gave rise to the products in moderate to good yields (Table 3).

Table 3 Synthesis of thiazolidin-2-ones



2 **1**

Entry	Thiazolidine-2-thione **2**	R^1	R^2	R^3	Reaction Conditions	Yield (%)
1	**2a**	H	H	H	4 h, 80 °C	60
2	**2b**	(*S*)-Me	H	H	4 h, 80 °C	66
3	**2c**	(*S*)-Ph	H	H	4 h, 60 °C	70
4	**2d**	(*S*)-*i*Pr	H	H	5 h, 60 °C	85
5	**2e**	(*S*)-*i*Bu	H	H	4 h, 60 °C	73
6	**2f**	(*S*)-Bn	H	H	5 h, 60 °C	73
7	**2g**	H	(*R*)-Ph	H	4 h, 60 °C	71
8	**2h**	H	H	(±)-Me	4 h, 60 °C	67
9	**2i**	H	H	(*R*)-Ph	4 h, 60 °C	79
10	**2j**	Me	Me	H	4 h, 60 °C	74
11	**2k**	H	$CH_2CH_2CH_2CH_2$		4 h, 60 °C	79

Biological Activities

The antibiotic activity of all synthetic compounds was assayed with ciprofloxacin and amphotericin B as positive controls (see Supplemental Materials, Table S1).

CONCLUSION

In conclusion, we have achieved the synthesis of various substituted thiazolidine-2-ones from corresponding thiazolidine-2-thiones and bromoethanol. The reaction process and mechanism were reinvestigated and verified through meticulous works and careful spectral analysis. The current procedure provides an efficient synthetic method of substituted thiazolidin-2-ones. The bioassay indicated that (*S*)-4-isobutyl and (*S*)-4-benzylthiazolidin-2-ones show certain inhibitive activities against *Candida albicans* and *Escherichia coli*.

EXPERIMENTAL

General

Melting points were obtained on a Yanaco MP-500 melting point apparatus and are uncorrected. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Mercury 200, Varian Mercury 300 Plus, or Bruker 400 spectrometer with tetramethylsilane (TMS) as an internal standard in $CDCl_3$ solution and the chemical shifts (δ) are reported in ppm. The IR spectra were taken on a Nicolet 5700 Fourier transform infrared (FTIR) spectrometer. HRMS data were determined using an Agilent LC/MSD TOF mass spectrometer. TLC separations were performed on silica gel GF_{254} plates, and the plates were visualized with UV light. Optical rotations were measured on a PE340C polarimeter with a thermally jacketed 10-cm cell (concentration *c* expressed as g/100 mL). All of the thiazolidine-2-thiones were

synthesized according to our reported protocol.[21] PE and EA are abbreviations for petroleum ether (50–90 °C) and ethyl acetate, respectively.

General Procedure for the Preparation of Thiazolidin-2-Ones

Sodium (230 mg, 10 mmol) was added to anhydrous EtOH (10 mL) to generate the sodium ethanolate, and then a thiazolidine-2-thione (10 mmol) and bromoethanol (1.75 g, 14 mmol) or chloroethanol (1.13 g, 14 mmol) was added to the solution. The resulting solution was heated at 60–80 °C in an oil bath for 3–5 h and then cooled to r.t. After filtration of the inorganic salt (NaBr or NaCl) and removal of the solvent, the residue was purified via column chromatography or recrystallization to obtain the desired products. The characterization data for the compounds are given below together with additional characterization data that may not have appeared in previous reports.

Thiazolidin-2-one (1a). Colorless crystals, yield 70%; m.p. 50–52 °C (ether). Lit.[11] m.p. 50–52 °C.

(*S*)-4-Methylthiazolidin-2-one (1b). Colorless crystals, yield 76%; lit.[22] m.p. 44–44.5 °C (ether).

(*S*)-4-Phenylthiazolidin-2-one (1c). Colorless crystals, yield 75%; lit.[14b] m.p. 175–176 °C (PE-EA). m.p. 175–176 °C.

(*S*)-4-Isopropylthiazolidin-2-one (1d). Colorless crystals, yield 85%; m.p. 89.5–92 °C (hexane-ether). R_f = 0.32 (PE: EA = 3:1, *v/v*); $[\alpha]^{20}_D$ = +6.90 (*c*, 1.10, Me_2CO); IR ($CHCl_3$) *v* (cm^{-1}): 1664; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.72 (br s, 1H, NH), 3.64 (td, *J* = 8.2, 7.4, 6.8 Hz, 1H, CHN), 3.35 (dd, *J* = 10.9, 7.4 Hz, 1H in CH_2S), 3.17 (dd, *J* = 10.9, 8.2 Hz, 1H in CH_2S), 1.84 (dheptet, *J* = 6.8, 6.8 Hz, 1H, CH in *i*Pr), 1.01 (d, *J* = 6.8 Hz, 3H, CH_3), 0.97 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 175.8, 61.4, 32.6, 32.5, 18.8, 18.2. HRMS (electrospray ionization [ESI]): Anal. Calcd. for $C_6H_{12}NOS$ $[M+H]^+$ *m/z*: 146.0636. Found: 146.0639.

(*S*)-4-Isobutylthiazolidin-2-one (1e). Colorless crystals, yield 73%; m.p. 61–64 °C (PE). R_f = 0.33 (PE: EA = 4:1, *v/v*); $[\alpha]^{20}_D$ = +15.9 (*c*, 1.4, Me_2CO); IR ($CHCl_3$) *v* (cm^{-1}): 1674; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.82 (br s, 1H, NH), 4.04–3.87 (m, 1H, CHN), 3.44 (dd, *J* = 10.8, 7.1 Hz, 1H in CH_2S), 3.07 (dd, *J* = 10.8, 7.5 Hz, 1H in CH_2S), 1.77–1.56 (m, 2H, CH & 1H in CH_2), 1.51–1.31 (m, 1H in CH_2), 0.95 (d, *J* = 6.4 Hz, 6H, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 175.7, 53.7, 43.9, 35.2, 25.0, 22.7, 22.1. HRMS (ESI): Anal. Calcd. for $C_7H_{14}NOS$ $[M+H]^+$ *m/z*: 160.0790. Found 160.0790.

(*S*)-4-Benzylthiazolidin-2-one (1f). Colorless crystals, yield 73%; 3% yield at lit.[23] m.p. 72–74 °C (PE-EA).

(*R*)-4-Phenylthiazolidin-2-one (1g). Colorless crystals, yield 71%; m.p. 175.5–177.5 °C (EtOH). Lit.[14b] m.p. 175–176 °C.

(±)-5-Methylthiazolidin-2-one (1h). Colorless crystals, yield 67%; m.p. 38–39.5 °C (ether), lit.[24] m.p. 39 °C.

(*R*)-5-Phenylthiazolidin-2-one (1i). lit.[8a]: Colorless crystals, yield 79%; m.p. 132.5–134 °C (PE-EA). R_f = 0.43 (PE: EA = 3:2, *v/v*); $[\alpha]^{20}_D$ = +81.2 (*c*, 0.5, Me_2CO); IR (CH_2Cl_2) *v* (cm^{-1}): 1673; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.39 (m, 5H, ArH), 6.79 (br s, 1H, NH), 5.05 (dd, *J* = 8.1, 7.7 Hz, 1H, CHS), 3.92 (dd, *J* = 10.2, 7.7 Hz, 1H in CH_2N), 3.66 (dd, *J* = 10.2, 8.1 Hz, 1H in CH_2N); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 175.8, 138.6, 128.9, 128.4, 127.4, 51.1, 50.3.

4,4-Dimethylthiazolidin-2-one (1j). Colorless crystals, yield 74%; m.p. 101.5–103.5 °C (PE-ether). R_f = 0.38 (PE: EA = 2:1, *v/v*); IR (CH_2Cl_2) *v* (cm^{-1}): 1676;

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 6.96 (br s, 1H, NH), 3.20 (s, 2H, CH_2S), 1.42 (s, 6H, $2CH_3$); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 174.3, 57.9, 42.1, 27.8. Anal. Calcd. for C_5H_9NOS: C, 45.77; H, 6.91; N, 10.68. Found: C, 45.80; H, 6.83; N, 10.69.

***cis*-(±)-7,9-Thiazabicyclo[4.3.0]nonane-8-one (1k).** Colorless crystals, yield 74%; m.p. 71.5–72 °C (hexane). Lit.[17] m.p. 51–52 °C.

General Procedure for the Preparation of Intermediates 3

Sodium (230 mg, 10 mmol) was added in anhydrous EtOH (10 mL) to generate the sodium ethanolate in an ice-water bath, and then thiazolidine-2-thione (10 mmol) and bromoethanol (1.75 g, 14 mmol) or chloroethanol (1.13 g, 14 mmol) were added to the above solution. The resulting solution was reacted at r.t. for 2 h. After the filtration of inorganic salt (NaBr or NaCl) and removal of the solvent, the residue was purified via column chromatography.

(*S*)-2-(2-Hydroxyethylthio)-4-phenylthiazoline (5c). Colorless crystals, yield 80%, m.p. 46.5–47.5 °C (PE-EA), $R_f = 0.54$ (PE: EA = 3:2, *v/v*), $[\alpha]^{20}_D = +199.5$ (*c*, 0.63, Me_2CO); IR (CH_2Cl_2) ν (cm^{-1}): 1556 ($\nu_{C=N}$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.40–7.28 (m, 5H, ArH), 5.45 (dd, $J = 9.3$, 8.2 Hz, 1H, CHN), 4.44 (br s, 1H, OH), 3.92 (br s, 2H, CH_2O), 3.80 (dd, $J = 10.9$, 8.2 Hz, 1H in CH_2S), 3.35 (dd, $J = 10.9$, 9.3 Hz, 1H in CH_2S), 3.31–3.20 (m, 2H, CH_2S); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 169.0, 140.8, 128.7, 127.8, 126.3, 79.0, 63.1, 43.4, 36.0. HRMS (ESI), Anal. Calcd. for $C_{11}H_{14}NOS_2^+$ $[M+H]^+$ m/z: 240.0511. Found: 240.0520.

(*S*)-2-(2-Hydroxyethylthio)-4-isobutylthiazoline (5e). Colorless oil, yield 82%. $R_f = 0.40$ (PE: EA = 4:1, *v/v*). $[\alpha]^{20}_D = -19.7$ (*c*, 0.88, Me_2CO); IR (CH_2Cl_2) ν (cm^{-1}): 1558 ($\nu_{C=N}$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.10 (br s, 1H, OH), 4.52–4.34 (m, 1H, CHN), 4.03–3.84 (m, 2H, CH_2O), 3.52 (dd, $J = 10.7$, 7.8 Hz, 1H in CH_2S), 3.23 (dd, $J = 6.1$, 4.1 Hz, 1H in CH_2S), 3.20 (dd, $J = 5.7$, 3.9 Hz, 1H in CH_2S), 3.09 (dd, $J = 10.7$, 8.3 Hz, 1H in CH_2S), 1.76 (m, 2H, CH & 1H in CH_2 at *i*Bu), 1.39 (ddd, $J = 7.0$, 7.0, 7.0 Hz, 1H in CH_2 at *i*Bu), 0.98 (d, $J = 6.7$ Hz, 3H, CH_3), 0.96 (d, $J = 6.8$ Hz, 3H, CH_3); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 166.9, 74.4, 63.6, 43.7, 41.2, 36.1, 25.9, 22.8, 22.4. HRMS (ESI), Anal. Calcd. for $C_9H_{18}NOS_2^+$ $[M+H]^+$ *m/z*: 220.0824. Found: 220.0831. Anal. Calcd. for $C_9H_{18}NOS_2$: C, 49.28; H, 7.81; N, 6.39. Found: 49.56, H, 7.73, N, 6.68.

***N*-(2-Hydroxyethyl)-4-phenylthiazolidine-2-thione (5c′).** Colorless oil, yield 3%, $R_f = 0.36$ (PE: EA = 3:2, *v/v*). $[\alpha]^{20}_D = +12.4$ (*c*, 0.45, Me_2CO); IR (CH_2Cl_2) ν (cm^{-1}): 1491 ($\nu_{C(S)-N}$), 1261 ($\nu_{C=S}$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.47–7.29 (m, 5H, ArH), 5.51 (dd, $J = 8.8$, 5.5 Hz, 1H, CHN), 4.40 (ddd, $J = 14.2$, 5.8, 4.0 Hz, 1H in CH_2O), 3.93 (ddd, $J = 11.4$, 7.4, 4.0, 1H in CH_2S), 3.82 (dd, $J = 11.2$, 8.8 Hz, 1H), 3.72 (ddd, $J = 11.4$, 5.8, 4.1, 1H in CH_2S), 3.198 (ddd, $J = 14.2$, 7.4, 4.1 Hz, 1H in CH_2O), 3.196 (dd, $J = 11.2$, 5.5 Hz, 1H in CH_2S). 2.37 (br s, 1H, OH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 198.3, 138.0, 129.4, 129.2, 126.8, 72.8, 58.4, 49.5, 35.9. HRMS (ESI), Anal. Calcd. for $C_{11}H_{14}NOS_2^+$ $[M+H]^+$ m/z: 240.0511. Found: 240.0520.

General Procedure for the Measurement of Antibacterial Activity

A pure culture of *C. albicans* (ATCC-10231) and *E. coli* (ATCC 25922) was grown overnight, and then diluted to a concentration of about 1×10^8 cfu/mL. The diluted microbial suspension was spread by a sterile swab on a Kirby-Bauer plate. The 1.0-mg sample was dissolved in chloroform and applied to the center of Whatman filter paper discs approximately 6 mm in diameter. The discs were placed onto the surface of the

inoculated agar plate. After 24 h in the incubator at 35 °C, the diameter of the zone of inhibition was measured. Supported by the National Natural Science Foundation of China (Nos. 20972013 and 20772005), Beijing Natural Science Foundation (No. 2092022), and the Scientific Research Foundation of Graduate School of Beijing University of Chemical and Technology

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