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REACTION OF 1-AZABICYCLO[1.1.0]BUTANE WITH ACTIVATED AMIDES

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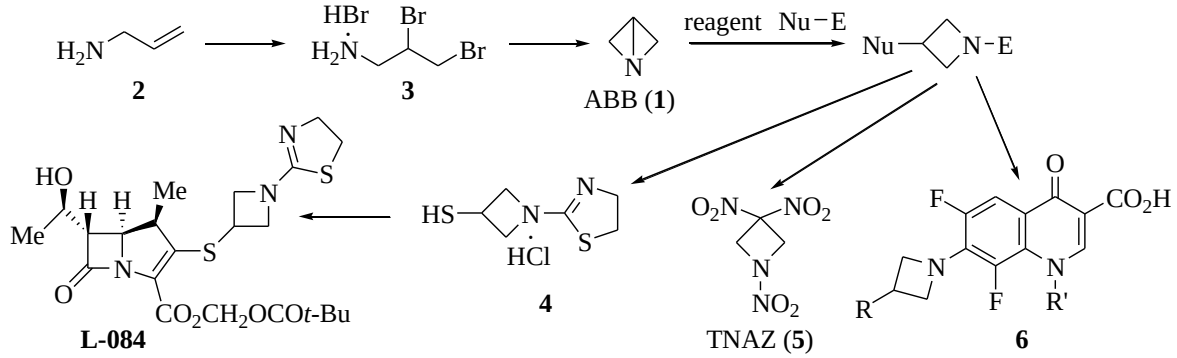
Abstract — 1-Azabicyclo[1.1.0]butane (ABB, **1**) reacted with 3-acyl-1,3-thiazolidine-2-thiones (**7**,**11a—m**) in the presence of a catalytic amount of $Mg(OTf)_2$ to give the corresponding 2-(1-acylazetidin-3-yl)thio-1,3-thiazolines (**8**,**12a—m**). It was hypothesized that this reaction is primarily influenced by a steric bulkiness of acyl groups in 3-acyl-1,3-thiazolidine-2-thiones. Resulting compounds (**8**, **12k**) were readily converted to thiols (**13**,**14**), and azetidine-3-thiol hydrochloride (**15**), which is the key intermediate of 1-(1,3-thiazolin-2-yl)azetidine-3-thiol hydrochloride (**4**) useful for the preparation of a new oral 1β-methylcarbapenem antibiotic **L-084**, was obtained quantitatively by hydrolysis of **14**.

INTRODUCTION

1-Azabicyclo[1.1.0]butanes have proved to be a unique molecule bearing a highly strained bicyclic structure, and are synthetically useful for the preparation of azetidine derivatives.[1,2] In the last two decades, numerous reactions have been described in which 1-azabicyclo[1.1.0]butanes were explored as versatile reagents.[1-3] However, the synthetic utility of unsubstituted 1-azabicyclo[1.1.0]butane (ABB, **1**), which must be useful for the preparation of various 3-monosubstituted and 1,3-disubstituted azetidines, has rarely been reported because of its synthetic difficulty related to its remarkably strained structure.[1,2] These azetidine moieties have often been found in many natural products[4] and biologically active compounds such as carbapenems[4] and new quinolone antibiotics.[5]

In this context, we established an efficient synthetic method of ABB (**1**) starting from allylamine (**2**) *via* 2,3-dibromopropylamine hydrobromide (**3**),[5] and reported its application to the syntheses of various 3-substituted azetidines.[7] Additionally, the resulting azetidines were converted to 1-(1,3-thiazolin-2-yl)azetidine-3-thiol hydrochloride (**4**), which was exploited for the synthesis of a new oral 1β-methylcarbapenem antibiotic **L-084**,[5,7,8] an energetic material 1,3,3-trinitroazetidine (TNAZ, **5**),[2,8] and a new quinolone derivatives (**6**),[9] as shown in Scheme 1. In the present study, we observed that the reaction of ABB (**1**) with activated amides results in electrophilic addition of the amides to afford 1,3-disubstituted azetidines, and this reaction is promoted by some Lewis acids. Herein, we focus on the reaction of ABB (**1**) with 3-acyl-1,3-thiazolidine-2-thiones as activated amides,[10] and report the results of our studies.

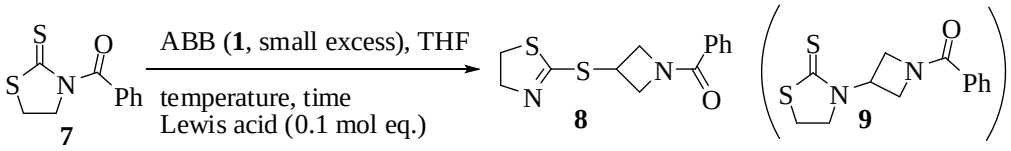


Scheme 1

RESULTS AND DISCUSSION

A THF solution of ABB (**1**), obtained by treatment of **3** with *n*-BuLi at -78 ºC in THF followed by codistillation with THF,[5,7] was used for the reaction with 3-acyl-1,3-thiazolidine-2-thiones. First, 3-benzoyl-1,3-thiazolidine-2-thione (**7**) was allowed to react with a small excess of ABB (**1**) under reflux for 15 h, and 2-(1-benzoylazetidin-3-yl)thio-1,3-thiazoline (**8**) was generated in poor yield, as shown in Scheme 2 and Table 1 (entry 1). The addition of the catalytic amount of Lewis acid improved the reaction, and $Mg(OTf)_2$ was most effective (entries 2—6). Room temperature was selected as the reaction temperature from the results of entries 6—8. The compound 1-(1-benzoylazetidin-3-yl)-1,3-thiazolidine-2-thione (**9**) was not obtained under any of the conditions employed (Scheme 2). In this reaction, the benzoyl group activated by a Lewis acid may initiate attack of the N1 position of the strained molecule ABB (**1**), followed by cleavage of the highly strained N1-C3 σ-bond,[2,11] and the sulfur atom of 1,3-thiazolidine-2-thionyl anion (**10**) then reacts with the cationic C3 position, as shown in Scheme 3.

Table 2 shows representative results of the reaction of ABB (**1**) with various 3-acyl-1,3-thiazolidine-2-thiones (**11a—m**) at room temperature in the presence of $Mg(OTf)_2$. All reactions proceeded to give the corresponding products **12a—m**. In the case of the reaction with **11a—h**,

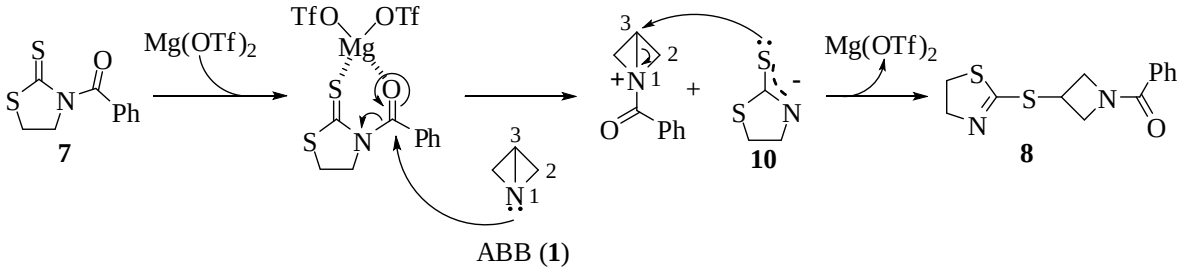


Scheme 2

Table 1 Reaction of ABB (**1**) with **7**

entry	Lewis acid	temperature	time (h)	yield (%)[a] of **8**
1	none	reflux	15	7
2	$Zn(OTf)_2$	reflux	15	21
3	$BF_3 \cdot Et_2O$	reflux	15	60
4	$Ti(O\textit{i}\text{-}Pr)_4$	reflux	4	60
5	$Mg(ClO_4)_2$	reflux	15	53
6	$Mg(OTf)_2$	reflux	0.5	65
7	$Mg(OTf)_2$	rt	1.5	64 (65)[b]
8	$Mg(OTf)_2$	0 ℃	15	62

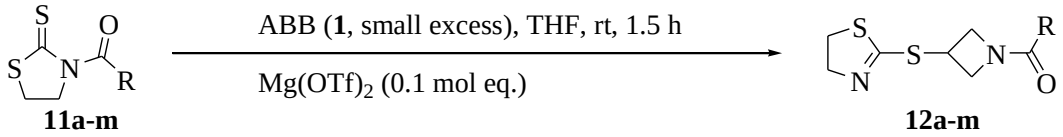
a) Determined by HPLC analysis (ODS column, 1 / 15 M phosphate buffer (pH 7.0) / MeCN = 60 / 40, at 254 nm). b) Isolated yield.



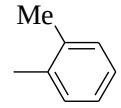
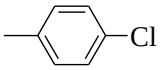
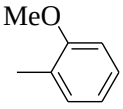
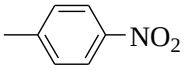
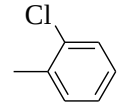
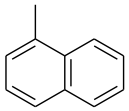
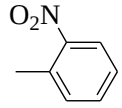
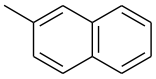
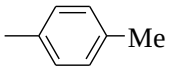
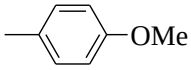
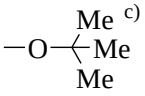
Scheme 3

para-substituted compounds **11e—h** showed a higher yield than the *ortho*-substituted compounds **11a—d** regardless of any electronic effect of the substituent on the aromatic ring (entries 1—8). The yield of the reaction with 3-(2-naphthoyl)-1,3-thiazolidine-2-thiones (**11j**) was higher than that of the reaction with 3-(1-naphthoyl)-1,3-thiazolidine-2-thiones (**11i**) (entries 9,10). The compound **11m** afforded **12m** in poor yield, compared with **11k** and **11l** (entries 11—13). From these results, it was estimated that this reaction with **11a—m** is mainly influenced not by an electronic effect but by the steric bulkiness of the acyl groups in 3-acyl-1,3-thiazolidine-2-thiones (**11a—m**).

Table 2 Reaction of ABB (**1**) with 3-acyl-1,3-thiazolidine-2-thiones **11a—m**

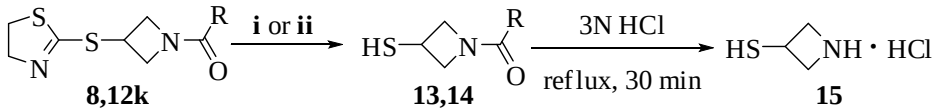


11a-m **12a-m**

entry	R		yield(%)[a] of **12a-m**		entry	R		yield (%)[a] of **12a-m**	
1		**12a**	34		7		**12g**	72	
2		**12b**	42		8		**12h**	58	
3		**12c**	46		9		**12i**	45	
4		**12d**	33		10		**12j**	61	
5		**12e**	57		11	—Me	**12k**	57	
					12	—H[b]	**12l**	52	
6		**12f**	71		13		**12m**	27	

a) Isolated yield. b) Reaction was carried out for 4 h. c) Reaction was carried out for 23 h.

Subsequently, the reaction of products **8** and **12k** with hydrochloric acid in MeOH were carried out under reflux, and thiols **13** and **14** were obtained in 80% and 75% yield, respectively (Scheme 4). To the best of our knowledge, 1-acylazetidine-3-thiols such as **13** and **14** have not been reported. This method is efficient for the synthesis of 1-acylazetidine-3-thiol derivatives. Further, the resulting compound **14** was readily hydrolyzed with 3N HCl to afford azetidine-3-thiol hydrochloride (**15**), which is the key intermediate of **4** (Scheme 1), in quantitative yield.



8,12k **13,14** **15**

8: R = Ph
12k: R = Me

13: R = Ph 80% yield
14: R = Me 75% yield

99% yield from **14**

Reagents and conditions: (**i**) 3N HCl - MeOH (1 : 10), reflux, 1 h; (**ii**) 1N HCl - MeOH (1 : 10), reflux, 40 min.

Scheme 4

In conclusion, we demonstrated the reaction of ABB (**1**) with 3-acyl-1,3-thiazolidine-2-thiones (**7, 11a-m**). The reaction was promoted by a Lewis acid, and 2-(1-acylazetidin-3-yl)thio-1,3-thiazolines (**8**, **12a-m**) were obtained. The resulting compounds (**8**, **12k**) were readily converted to thiols (**13**, **14**), respectively. The compound (**14**) was hydrolyzed quantitatively to give **15**, which is the key intermediate of **4** useful for the preparation of **L-084**.

EXPERIMENTAL

All melting points were measured using a Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained on a JASCO FT/IR-420 or JASCO FT/IR-4100 IR Fourier transform spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-ECA500 (500 MHz) spectrometer. ^{13}C-NMR spectra were recorded on a JEOL JNM-ECA500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as an internal standard. Electron spray ionization (ESI)-MS were recorded on a Waters LCT Premier spectrometer. All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel [Kanto Chemical 60N (spherical, neutral); 63-210 μm]. All reagents were used as purchased.

THF solution of 1-azabicyclo[1.1.0]butane (ABB, 1)[5,7,8]

A hexane solution of *n*-BuLi (2.64 mol/L, 94.7 ml, 252 mmol) was added dropwise to a suspension of **3** (25.0 g, 83.9 mmol) in THF (250 mL) at -78 ºC under nitrogen, and the mixture was stirred at -78 ºC for 1 h. The reaction was then quenched with 50% KOH and distilled at 80 ºC. The resulting THF solution was dried over K_2CO_3 and filtered. The filtrate was adjusted to the 500 mL volume with THF. This THF solution of ABB (**1**, *ca.* 0.14 mol/L) was used in the following reactions.

Typical procedure for the preparation of 2-(1-benzoylazetidin-3-yl)thio-1,3-thiazoline (8) (Table 1)

To a solution of 3-benzoyl-1,3-thiazolidine-2-thione (**7**, 139 mg, 0.621 mmol) and ABB (**1**, *ca.* 0.14 mol/L in THF, 5.0 mL, *ca.* 0.70 mmol) in THF was added $Mg(OTf)_2$ (20 mg, 0.062 mmol) at 0 ºC. After being stirred at room temperature for 1.5 h, the reaction mixture was evaporated *in vacuo* to give a residue, which was purified by column chromatography on silica gel with *n*-hexane – AcOEt (1 : 2, v/v) to afford **8** (113 mg, 65%).

2-(1-Benzoylazetidin-3-yl)thio-1,3-thiazoline (**8**): Colorless needles (Et_2O); mp 92—92.5 ºC; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.40 (2H, t, *J* = 8.0 Hz), 4.10—4.30 (2H, m), 4.17 (2H, td, *J* = 8.0, 2.3 Hz), 4.43 (1H, tt, *J* = 8.0, 5.5 Hz), 4.56—4.78 (2H, m), 7.41 (2H, t, *J* = 7.4 Hz), 7.47 (1H, t, *J* = 7.4 Hz), 7.62 (2H, d, *J* = 7.4 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 33.9, 35.7, 54.8, 61.0, 64.4, 127.9, 128.4, 131.2, 132.7, 163.3, 170.4; IR (KBr) 1629, 1565, 1446, 1400, 1002, 792, 717, 695 cm^{-1}; ESI-MS Calcd for $C_{13}H_{14}N_2OS_2$ MW 279.0626, Found *m/z* 279.0626 (M^+ + H).

Typical procedure for the preparation of 2-(1-acylazetidin-3-yl)thio-1,3-thiazoline 12 (Table 2)

To a solution of 3-(2-methyl)benzoyl-1,3-thiazolidine-2-thione (**9k**, 60 mg, 0.37 mmol) and ABB (**1**, *ca.* 0.14 mol/L in THF, 3.0 mL, *ca.* 0.42 mmol) in THF was added $Mg(OTf)_2$ (12 mg, 0.037 mmol) at 0 ºC. After being stirred at room temperature for 1.5 h, the reaction mixture was evaporated *in vacuo* to give a residue, which was purified by column chromatography on silica gel with *n*-hexane – AcOEt (1 : 2, v/v) to $CHCl_3$ – MeOH (10 :1, v/v) to afford **10k** (46 mg, 57%).

2-[1-(2-Methylbenzoyl)azetidin-3-yl]thio-1,3-thiazoline (**12a**): Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.40 (3H, s), 3.39 (2H, td, *J* = 8.0, 2.3 Hz), 3.83—3.92 (1H, m), 4.11—4.19 (1H, m), 4.15 (2H, t, *J* = 8.0 Hz), 4.32—4.41 (2H, m), 4.55—4.62 (1H, m), 7.16—7.26 (3H, m), 7.29 (1H, td, *J* = 7.5, 1.7 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 19.3, 33.4, 35.6, 54.2, 59.0, 64.2, 125.6, 126.6, 129.7, 130.8, 133.4, 135.5, 163.6, 171.3; IR (neat) 2945, 2877, 1643, 1570, 1415, 742 cm^{-1}; ESI-MS Calcd for $C_{14}H_{17}N_2OS_2$ MW 293.0782, Found *m/z* 293.0784 (M^+ + H).

2-[1-(2-Methoxybenzoyl)azetidin-3-yl]thio-1,3-thiazoline (**12b**): Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.38 (2H, td, *J* = 8.0, 2.9 Hz), 3.86 (3H, s), 3.89—3.94 (1H, m), 4.09—4.14 (1H, m), 4.16 (2H, t, *J* = 8.0 Hz), 4.36—4.45(2H, m), 6.91 (1H, d, *J* = 7.4 Hz), 6.98 (1H, t, *J* = 7.4 Hz), 7.37 (1H, t, *J* = 7.4 Hz), 7.38 (1H, d, *J* = 7.4 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 33.5, 35.6, 54.6, 55.7, 58.4, 64.2, 111.2, 120.8, 123.3, 129.2, 131.5, 156.0, 163.9, 168.9; IR (neat) 2943, 2879, 1633, 1570, 1464, 1441, 1248, 1022, 756 cm^{-1}; ESI-MS Calcd for $C_{14}H_{17}N_2O_2S_2$ MW 309.0731, Found *m/z* 309.0730 (M^+ + H).

2-[1-(2-Chlorobenzoyl)azetidin-3-yl]thio-1,3-thiazoline (**12c**): Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.39 (2H, td, *J* = 8.0, 2.3 Hz), 3.87—3.94 (1H, m), 4.10—4.19 (1H, m), 4.15 (2H, t, *J* = 8.0 Hz), 4.35—4.45 (2H, m), 4.56—4.65 (1H, m), 7.23—7.42 (4H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 33.4, 35.6, 54.5, 58.3, 64.2, 127.0, 128.4, 129.8, 130.5, 130.8, 133.6, 163.3, 167.8; IR (neat) 2945, 2877, 1651, 1568, 1423, 1059, 748 cm^{-1}; ESI-MS Calcd for $C_{13}H_{14}ClN_2OS_2$ MW 313.0236 Found *m/z* 313.0238 (M^+ + H).

2-[1-(2-Nitrobenzoyl)azetidin-3-yl]thio-1,3-thiazoline (**12d**): Pale yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.39 (2H, td, *J* = 8.0, 4.6 Hz), 3.85 (1H, dd, *J* = 9.2, 5.5 Hz), 4.12—4.22 (1H, m), 4.15 (2H, t, *J* = 8.0 Hz), 4.33 (1H, dd, *J* = 9.2, 8.0 Hz), 4.46 (1H, tt, *J* = 8.0, 5.5 Hz), 4.67 (1H, dd, *J* = 10.9, 8.0 Hz), 7.45 (1H, d, *J* = 7.8 Hz), 7.59 (1H, t, *J* = 7.8 Hz), 7.70 (1H, t, *J* = 7.8 Hz), 8.15 (1H, d, *J* = 7.8 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 33.5, 35.6, 54.9, 58.5, 64.3, 124.7, 128.5, 130.4, 130.7, 134.2, 145.9, 163.2, 167.7; IR (neat) 2947, 2877, 1651, 1574, 1531, 1485, 1427, 1348, 760 cm^{-1}; ESI-MS Calcd for $C_{13}H_{13}N_3NaO_3S_2$ MW 346.0296, Found *m/z* 346.0300 (M^+ + Na).

2-[1-(4-Methylbenzoyl)azetidin-3-yl]thio-1,3-thiazoline (**12e**): Colorless needles (THF–*n*-hexane); mp 140—141 ºC; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.38 (3H, s), 3.40 (2H, t, *J* = 8.0 Hz), 4.09—4.29 (2H, m), 4.17 (2H, t, *J* = 8.0 Hz), 4.42 (1H, tt, *J* = 8.0, 5.4 Hz), 4.55—4.78 (2H, m), 7.21 (2H, d, *J* = 8.0 Hz), 7.52

(2H, d, *J* = 8.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.4, 33.9, 35.6, 54.8, 61.0, 64.3, 127.9, 129.0, 129.8, 141.6, 163.6, 170.4; IR (KBr) 2939, 1624, 1568, 1415, 833, 750 cm^{-1}; ESI-MS Calcd for $C_{14}H_{17}N_2OS_2$ MW 293.0782, Found *m/z* 293.0780 (M^+ + H).

2-[1-(4-Methoxybenzoyl)azetidin-3-yl]thio-1,3-thiazoline (**12f**): Colorless plates (THF–*n*-hexane); mp 116—117 ºC; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.40 (2H, t, *J* = 8.0 Hz), 3.86 (3H, s), 4.08—4.32 (2H, m), 4.17 (2H, t, *J* = 8.0 Hz), 4.42 (1H, tt, *J* = 8.0, 5.5 Hz), 4.53—4.81 (2H, m), 6.88—6.96 (2H, m), 7.57—7.66 (2H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 33.9, 35.6, 54.8, 55.3, 61.2, 64.2, 113.6, 124.9, 129.8, 161.9, 163.8, 170.0; IR (KBr) 2941, 1606, 1574, 1423, 1402, 1257, 1028, 845, 764 cm^{-1}; ESI-MS Calcd for $C_{14}H_{17}N_2O_2S_2$ MW 309.0731, Found *m/z* 309.0738 (M^+ + H).

2-[1-(4-Chlorobenzoyl)azetidin-3-yl]thio-1,3-thiazoline (**12g**): Pale yellow needles (THF–*n*-hexane); mp 109.5—110.5 ºC; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.40 (2H, t, *J* = 8.0 Hz), 4.09—4.27 (2H, m), 4.17 (2H, t, *J* = 8.0 Hz), 4.43 (1H, tt, *J* = 8.0, 5.5 Hz), 4.54—4.77 (2H, m), 7.39 (2H, d, *J* = 8.3 Hz), 7.57 (2H, d, *J* = 8.3 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 33.9, 35.6, 54.8, 61.1, 64.0, 128.7, 129.3, 131.0, 137.4, 164.1, 169.2; IR (KBr) 2945, 1608, 1564, 1439, 1090, 841, 746 cm^{-1}; ESI-MS Calcd for $C_{13}H_{14}ClN_2OS_2$ MW 313.0236, Found *m/z* 313.0235 (M^+ + H).

2-[1-(4-Nitrobenzoyl)azetidin-3-yl]thio-1,3-thiazoline (**12h**): Pale yellow powder (THF–*n*-hexane); mp 140—142 ºC; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.41 (2H, t, *J* = 8.0 Hz), 4.12—4.27 (2H, m), 4.17 (2H, td, *J* = 8.0, 3.4 Hz), 4.45 (1H, tt, *J* = 8.0, 5.5 Hz), 4.58—4.76 (2H, m), 7.79 (2H, d, *J* = 8.6 Hz), 8.28 (2H, d, *J* = 8.6 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 33.8, 35.6, 54.9, 60.9, 64.2, 123.7, 128.9, 138.5, 149.3, 163.5, 168.0; IR (KBr) 2949, 1620, 1599, 1562, 1520, 1439, 1348, 843, 714 cm^{-1}; ESI-MS Calcd for $C_{13}H_{14}N_3O_3S_2$ MW 324.0477, Found *m/z* 324.0483 (M^+ + H).

2-[1-(1-Naphthoyl)azetidin-3-yl]thio-1,3-thiazoline (**12i**): Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.37 (2H, td, *J* = 8.0, 4.0 Hz), 3.86 (1H, dd, *J* = 9.2, 5.2 Hz), 4.13 (2H, t, *J* = 8.0 Hz), 4.26 (1H, dd, *J* = 10.6, 5.2 Hz), 4.33 (1H, dd, *J* = 9.2, 8.0 Hz), 4.39 (1H, tt, *J* = 8.0, 5.2 Hz), 4.70 (1H, dd, *J* = 10.6, 8.0 Hz), 7.47 (1H, dd, *J* = 8.0, 6.9 Hz), 7.51—7.61 (3H, m), 7.87 (1H, d, *J* = 8.0 Hz), 7.90 (1H, d, *J* = 8.0 Hz), 8.14 (1H, d, *J* = 8.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 33.5, 35.5, 54.6, 59.2, 64.2, 124.8, 125.2, 125.4, 126.4, 127.2, 128.4, 129.7, 130.4, 131.3, 133.6, 163.6, 170.7; IR (neat) 2945, 2877, 1643, 1570, 1425, 1385, 795, 779, 752 cm^{-1}; ESI-MS Calcd for $C_{17}H_{17}N_2OS_2$ MW 329.0782, Found *m/z* 329.0782 (M^+ + H).

2-[1-(2-Naphthoyl)azetidin-3-yl]thio-1,3-thiazoline (**12j**): Colorless plates (THF–*n*-hexane); mp 120.5—121.5 ºC; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.40 (2H, t, *J* = 8.0 Hz), 4.12—4.37 (2H, m), 4.17 (2H, td, *J* = 8.0, 1.7 Hz), 4.46 (1H, tt, *J* = 8.0, 5.0 Hz), 4.62—4.86 (2H, m), 7.51—7.62 (2H, m), 7.71 (1H, dd, *J* = 8.6, 1.8 Hz), 7.83—7.96 (3H, m), 8.11 (1H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 34.0, 35.6, 54.9, 61.2, 64.3, 124.4, 126.7, 127.6, 127.8, 128.3, 128.4, 128.8, 130.0, 132.5, 134.5, 163.6, 170.5; IR (KBr) 2924, 1631,

1608, 1568, 1444, 1423, 823, 775, 760 cm^{-1}; ESI-MS Calcd for $C_{17}H_{16}N_2NaOS_2$ MW 351.0602, Found *m/z* 351.0582 (M^+ + Na).

2-(1-Acetylazetidin-3-yl)thio-1,3-thiazoline (**12k**): Colorless plates (THF–*n*-hexane); mp 63—64 ºC; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.87 (3H, s), 3.41 (2H, t, *J* = 8.0 Hz), 3.93 (1H, dd, *J* = 9.7, 5.2 Hz), 4.07 (1H, dd, *J* = 8.9, 5.2 Hz), 4.19 (2H, td, *J* = 8.0, 2.3 Hz), 4.36 (1H, tt, *J* = 8.0, 5.2 Hz), 4.41 (1H, dd, *J* = 9.7, 8.0 Hz), 4.58 (1H, dd, *J* = 8.9, 8.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 18.8, 32.7, 35.7, 54.1, 58.2, 64.4, 163.4, 170.5; IR (KBr) 2945, 2877, 1631, 1567, 1463 cm^{-1}; ESI-MS Calcd for $C_8H_{13}N_2OS_2$ MW 217.0469, Found *m/z* 217.0477 (M^+ + H).

2-(1-Formylazetidin-3-yl)thio-1,3-thiazoline (**12l**): Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.42 (2H, t, *J* = 8.0 Hz), 3.93—4.00 (1H, m), 4.09—4.13 (1H, m), 4.19 (2H, t, *J* = 8.0 Hz), 4.42—4.51 (2H, m), 4.57—4.64 (1H, m), 8.00 (1H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 34.6, 35.7, 53.9, 55.8, 64.3, 161.9, 163.1; IR (neat) 2945, 1663, 1568, 1418, 1363 cm^{-1}; ESI-MS Calcd for $C_7H_{10}N_2NaOS_2$ MW 225.0132, Found *m/z* 225.0133 (M^+ + Na).

2-(1-*tert*-Butoxycarbonylazetidin-3-yl)thio-1,3-thiazoline (**12m**): Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.44 (9H, s), 3.40 (2H, t, *J* = 8.0 Hz), 3.88 (2H, dd, *J* = 9.5, 4.9 Hz), 4.19 (2H, t, *J* = 8.0 Hz), 4.26—4.39 (3H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.3, 33.2, 35.6, 37.7, 55.6, 57.3, 64.4, 79.8, 155.9, 163.6; IR (neat) 2976, 2883, 1703, 1568, 1456, 1392, 1367, 1157 cm^{-1}; ESI-MS Calcd for $C_{11}H_{19}N_2O_2S_2$ MW 275.0888, Found *m/z* 275.0869 (M^+ + H).

1-Benzoylazetidine-3-thiol (13)

To a solution of 2-(1-benzoylazetidin-3-yl)thio-1,3-thiazoline (**8**, 167 mg, 0.600 mmol) in MeOH (6 mL) was added dropwise 3N HCl (0.6 mL) at rt. After the mixture was refluxed for 1 h, the reaction mixture was concentrated *in vacuo* and then extracted with AcOEt. The extract was dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with *n*-hexane – AcOEt (1 : 1, v/v) to afford **13** (92 mg, 80%).

1-Benzoylazetidine-3-thiol (**13**): Colorless plates (THF–*n*-hexane); mp 73.5—75 ºC; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.08 (1H, d, *J* = 8.0 Hz), 3.77—3.86 (1H, m), 4.00—4.23 (2H, m), 4.60—4.73 (2H, m), 7.42 (2H, t, *J* = 7.5 Hz), 7.47 (1H, t, *J* = 7.5 Hz), 7.61 (2H, d, *J* = 7.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 27.6, 59.4, 63.8, 127.8, 128.4, 131.2, 132.7, 170.2; IR (KBr) 2947, 2866, 2501, 1611, 1574, 1448, 1431, 795, 716 cm^{-1}; ESI-MS Calcd for $C_{10}H_{12}NOS$ MW 194.0640, Found *m/z* 194.0631 (M^+ + H).

1-Acetylazetidine-3-thiol (14)

To a solution of 2-(1-acetylazetidin-3-yl)thio-1,3-thiazoline (**12k**, 2.16 g, 10.0 mmol) in MeOH (100 mL) was added dropwise 1N HCl (10 mL) at rt. After the mixture was refluxed for 40 min, the reaction mixture was concentrated *in vacuo*, and then extracted with AcOEt. The extract was dried over anhydrous

$MgSO_4$, filtered, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with *n*-hexane – AcOEt (1 : 2, v/v) to $CHCl_3$ – MeOH (10 : 1, v/v) to afford **14** (979 mg, 75%).

1-Acetylazetidine-3-thiol (**14**): Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.86 (3H, s), 2.06 (1H, d, *J* = 8.0 Hz), 3.74 (1H, qt, *J* = 8.0, 5.7 Hz), 3.85 (1H, dd, *J* = 9.7, 5.7 Hz), 3.98 (1H, dd, *J* = 8.6, 5.7 Hz), 4.44 (1H, dd, *J* = 9.7, 8.0 Hz), 4.54 (1H, dd, *J* = 8.6, 8.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 18.8, 26.5, 58.6, 61.1, 170.4; IR (neat) 2501, 1611, 1574, 1448, 1431, 795, 716 cm^{-1}; ESI-MS Calcd for $C_5H_{10}NOS$ MW 132.0483, Found *m/z* 132.0486 (M^+ + H).

Azetidine-3-thiol hydrochloride (15)[5(b),7]

1-Acetylazetidiene-3-thiol (**14**, 39 mg, 0.30 mmol) was dissolved in 3N HCl (3 mL), and the acidic solution was refluxed for 30 min. The reaction mixture was washed with AcOEt and evaporated *in vacuo* to afford **15** (37 mg, 99%).

Azetidine-3-thiol hydrochloride (**15**): Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.93—4.09 (3H, m), 4.38—4.45 (2H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 30.8, 57.4; IR (neat) 3734, 3649, 2972, 1541, 1457 cm^{-1}; ESI-MS Calcd for C_3H_7NNaS MW 112.0197, Found *m/z* 112.0196 (M^+ - HCl + Na).

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