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Novel efficient synthesis of 1-azabicyclo[1.1.0]butane and its application to the synthesis of 1-(1,3-thiazolin-2-yl)azetidine-3-thiol useful for the pendant moiety of an oral 1β-methylcarbapenem antibiotic L-084

Kazuhiko Hayashi, [†,‡] **Chisato Sato,** [‡] **Shinsuke Hiki,** [†] **Toshio Kumagai,** [‡] **Satoshi Tamai,** [‡] **Takao Abe,** [‡] **and Yoshimitsu Nagao*** [†]

[†] Faculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770-8505, Japan

[‡] The Medical Research Laboratories, Wyeth Lederle Japan, Ltd., Kashiwa-cho, Shiki-shi, Saitama 353-8511, Japan

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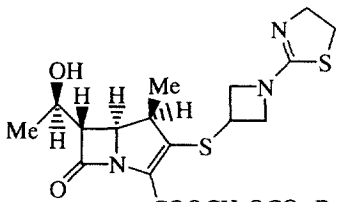
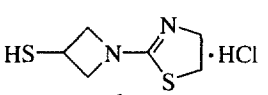
Abstract: 1-Azabicyclo[1.1.0]butane **2** was successfully synthesized by treatment of 2,3-dibromopropylamine hydrobromide **4** with organolithium compounds and was readily converted to 1-(1,3-thiazolin-2-yl)azetidine-3-thiol hydrochloride **1** and versatile azetidine derivatives **9** and **10**.

Keywords: aza compound; azetidines; cyclization; thiazolines

L-084, which was developed by a Wyeth Lederle Japan research group, is a new oral 1β-methylcarbapenem antibiotic with a broad spectrum and a potent antibacterial activity against various clinically isolated bacteria except for *P. aeruginosa*.[1] This antibiotic was synthesized by employing a particular heterocycle, 1-(1,3-thiazolin-2-yl)azetidine-3-thiol hydrochloride **1**. However, the synthetic procedure of **1** resulted in a low yield because of adopting a roundabout synthetic way from epichlorohydrin.[2] This disappointing result led us to pursue another route for the synthesis of **1**. In this report, we describe a novel synthetic method for a remarkably strained molecule, 1-azabicyclo[1.1.0]butane **2**, and its exploitation in an expeditious synthesis of **1** and other versatile azetidines.[3]



L-084



1

2

1-Azabicyclo[1.1.0]butane derivatives are regarded as unique molecules having the highly strained bicyclic structure.[4] Especially, 1-azabicyclo[1.1.0]butane **2** is synthetically useful as a synthon for the preparation of 1,3-disubstituted or 3-monosubustituted azetidines and as a starting compound for the synthesis of 1,3,3-trinitroazetidine .[4a,5] In spite of the compound's usefulness , only three reports on the synthesis of **2**

*Corresponding author. Fax : +81-88-633-9503, E-mail : ynagao@ph2.tokushima-u.ac.jp

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have appeared. Its synthesis was first recorded by Funke in 1969,[4a,b] in which the starting compound was expensive and the yield was 7%. In 1995, Paritosh reported a synthetic procedure of **2** producing a fairly good yield *via* 3-chloroazetidine derivatives from epichlorohydrin, though this procedure required many reaction steps.[6] Bartnik and Cal recently reported the synthesis of **2** by starting from inexpensive allylamine in a one-pot manner, but the yield of **2** was poor.[7] Thus, we, first of all, examined the reaction conditions for the synthesis of **2** starting from allylamine **3** *via* 2,3-dibromopropylamine hydrobromide **4**, as shown in Scheme1. Compound **4**[8] was readily prepared by conventional bromination in 95% yield, and its cyclization was attempted in the presence of various bases. All results are summarized in Table 1.

Scheme 1

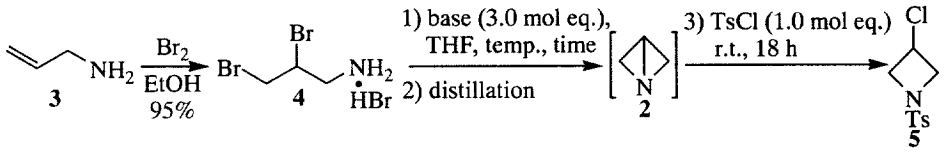


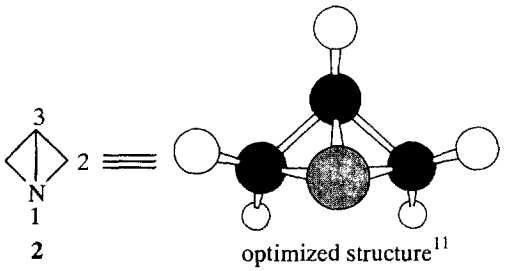
Table 1. Conversion of **4** to **5** *via* 1-azabicyclo[1.1.0]butane **2**.

entry	base	additive	temp.	time (h)	yield (%)[a] of **5**
1	KOH	non	reflux	1	2
2	LiOH	non	reflux	1.5	8
3	DBU	non	reflux	1	ND[c]
4	NaH	non	r.t.	18	ND[c]
5	LiH	non	r.t.	18	ND[c]
6	NaOMe	non	r.t.	24	2
7	KO^{t}Bu	non	r.t.	17	4
8	LiOMe	non	r.t.	18	4
9	$NaNH_2$	non	r.t.	18	ND[c]
10	$LiNH_2$	non	r.t.	18	34
11	LDA[b]	non	r.t.	18	39
12	*n*-BuLi	non	-78 °C	1	66
13	*n*-BuLi[b]	non	-78 °C	1	82
14	PhLi[b]	non	-78 °C	1	87
15	MeMgBr[b]	non	-78 °C	1	2
16	PhMgBr	non	-78 °C	1	1
17	*n*-BuLi[b]	12-crown-4 (3.0 mol eq.)	-78 °C	1	1
18	$LiNH_2$	12-crown-4 (3.0 mol eq.)	r.t.	18	ND[c]

a) Determined by HPLC analysis.[10] b) Quenched with 50% aq. KOH. c) Not detected.

We confirmed the structure of **2** by ^{1}H- and ^{13}C-NMR analyses (Fig. 1) and by its conversion to 1-tosyl-3-chloroazetidine **5**[4a] because of the difficulty of isolating pure **2** (bp 51 °C) from the THF (bp 65 °C) solution.[4a] The desirable cyclization proceeded only by the use of organolithium compounds and lithium amide, as shown in Table 1 (entries 10 – 14).[9] Interestingly, **2** was formed in the presence of $LiNH_2$, whereas it was not

obtained by employing $NaNH_2$ (entry 10 vs. 9). Further, the reaction of **4** with *n*-BuLi or $LiNH_2$ in the presence of a crown ether trapping a lithium cation resulted in almost no yield of **5** (entries 17 and 18). These results indicate that a lithium cation must play an important role in the cyclization of **4**; however, the exact reason for this and the reaction mechanism remain unclear.

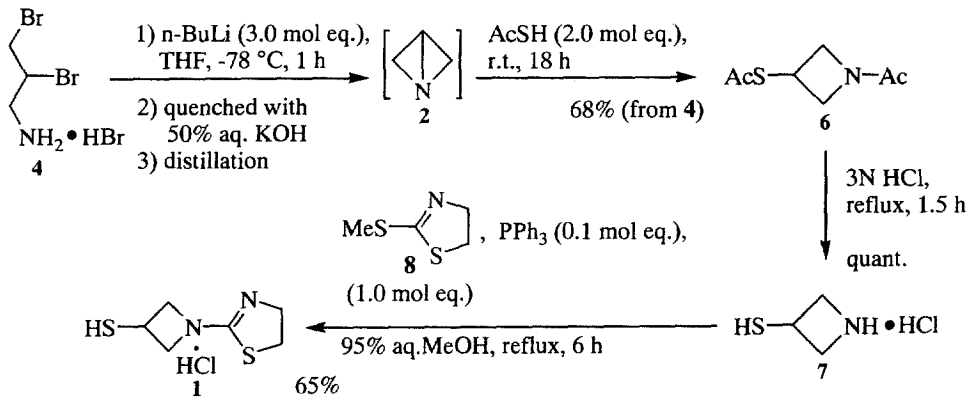


400MHz ^{1}H-NMR (THF-d8, δ ppm)	100MHz ^{13}C-NMR (THF-d8, δ ppm)
H-2 : 0.85 (m, 2 H)	C-2 : 17.2
2.07 (m, 2 H)	C-3 : 51.1
H-3 : 2.29 (m, 1 H)	

Figure 1. Optimized structure of **2** and its ^{1}H- and ^{13}C-NMR spectral data.

Subsequently, the synthesis of **1** was successfully performed using the synthetic route represented in Scheme 2. [12] Conversion of **2** to 1-acetyl-3-acetylthioazetidine **6**[13] was achieved by treatment of **2** with AcSH in 68% yield from **4**. The hydrolysis of **6** with 3N HCl under reflux gave azetidine-3-thiol hydrochloride **7**[14] in a quantitative yield. In the final step, the compound **1**[15] was obtained by the reaction with 2-methylthio-1,3-thiazoline **8** in the presence of a catalytic amount of PPh_3 in 65% yield. PPh_3 was employed for the reduction of the resulting disulfides. Because chromatographical purification is unnecessary in each reaction described above, this synthetic procedure is promising for the large-scale synthesis of **1**.

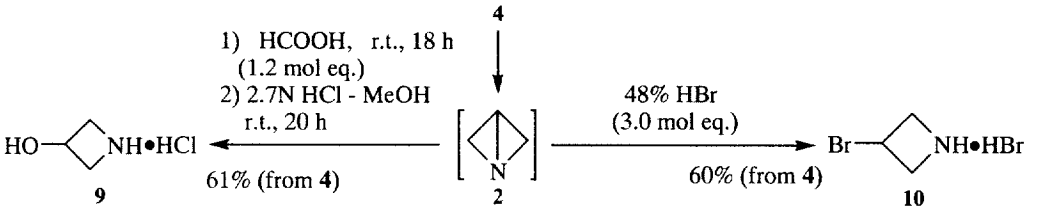
Scheme 2



Finally, we prepared versatile azetidine derivatives, as shown in Scheme 3. 3-Hydroxyazetidine hydrochloride **9**,[16] useful for the synthesis of some azetidine derivatives[17] (e.g. quinolone antibiotics), was readily obtained by treatment of **2** with formic acid followed by acidic hydrolysis. 3-Bromoazetidine hydrobromide **10**,[18] which can be exploited to prepare various 3-substituted azetidine derivatives *via* suitable nucleophilic substitution reactions, was also obtained by the reaction of **2** with 48% HBr.

In conclusion, we established an efficient method for synthesizing 1-azabicyclo[1.1.0]butane **2** by starting from allylamine **3** *via* bromination followed by cyclization with organolithiums. Further, a new heterocycle **1** useful for the synthesis of oral antibiotic **L-084** and other versatile azetidines were readily synthesized in satisfactory yields.

Scheme 3



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[8] Compound **4** : colorless prisms from MeOH, mp 176-178 °C; ^{1}H-NMR (400 MHz, CD_3OD) δ 3.38 (dd, J = 9.5, 13.9 Hz, 1 H), 3.70 (dd, J= 3.2, 13.9 Hz, 1 H), 3.94 (dd, J = 8.3, 11.0 Hz, 1 H), 4.01 (dd, J = 4.6, 11.0 Hz, 1 H), 4.52-4.60 (m, 1 H). Cf. Kimpe ND, Smaele DD, Bogaert P. *Synlett.* **1994**, 287.

[9] Preparation of 1-azabicyclo[1.1.0]butane **2** (entry 13 in Table 1) : A hexane solution of *n*-BuLi (50.4 mmol) was added dropwise to a suspension of **4** (5.00 g, 16.8 mmol) in anhydrous THF (50 ml) at -78 °C under argon, and the mixture was stirred at -78 °C for 1 h. Then the solution was quenched with 50% KOH aqueous solution and distilled at 80 °C. The resulting THF solution was dried over K_2CO_3 and filtered off followed by exact adjustment to the 100 ml volume with THF. This THF solution of 1-azabicyclo[1.1.0]butane **2** was used to prepare various azetidines.

[10] The yield of **5** was determined as follows: TsCl (160 mg, 0.84 mmol) was added to 5 ml of the THF solution of **2**[9] at 0 °C under argon and then the mixture was stirred at room temperature for 18 h. The reaction mixture was analyzed by means of HPLC (ODS column, 0.05 M phosphate buffer (pH 7.0) / MeCN = 50 / 50, at 254 nm).

[11] The structure of **2** was optimized by using the *ab initio* method at the HF/6-31G* level (MacSpartan PLUS 1.1.7, Wavefunction, Inc.), which will be reported in detail elsewhere.

[12] *n*-BuLi was used for the cyclization of **4** because of the reagent's lesser expensive than PhLi.

[13] Compound **6** : colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.86 (s, 3 H), 3.36 (s, 3 H), 4.8-5.7 (m, 5 H).

[14] Compound **7** : colorless oil; ^{1}H-NMR (200 MHz, CD_3OD) δ 3.9-4.2 (m, 3 H), 4.3-4.6 (m, 2 H).

[15] Compound **1** : colorless needles from MeCN-THF, mp 125-127 °C (decomp.); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.60 (dd, J = 8.6 Hz, 1 H), 3.60 (t, J= 7.3 Hz, 2 H), 3.9-4.2 (m, 1 H), 4.13 (t, J = 7.3 Hz, 2 H), 5.1-5.2 (m, 1 H), 12.11 (brs, 1 H).

[16] Compound **9** : colorless prisms from H_2O-MeOH, mp 80-81 °C, lit. mp 91-92 °C ; Chatterjee SS, Triggle DJ. *Chem. Commun.*, **1968**, 93.

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[18] Compound **10** : colorless needles from MeOH-AcOEt, mp 119 °C ; ^{1}H-NMR (200 MHz, CD_3OD) δ 4.26 (dd, J = 5.1, 12.4 Hz, 2 H), 4.74 (dd, J= 7.1, 12.4 Hz, 2 H), 4.8-5.0 (m, 1 H).