HETEROCYCLES, Vol. 56, 2002, pp. 433 - 442, Received, 29th August, 2001

SYNTHESIS OF AZETIDINE DERIVATIVES USING 1-AZABICYCLO[1.1.0]BUTANE†

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Abstract- A THF solution of 1-azabicyclo[1.1.0]butane (**2**), obtained from 2,3-dibromopropylamine hydrobromide (**1**), was treated with HCl-EtOH, 48% HBr, $ClCO_2Et$, Ts_2O, HCO_2H - 2.7N HCl-MeOH, or Ac_2O - 3N HCl to give the corresponding 3-monosubstituted and 1,3-disubstituted azetidine derivatives (**3**-**7**) . Similar treatment of **2** with AcSH afforded 1-acetyl-3-acetylthioazetidine (**8**), which was converted to 1-(1,3-thiazolidin-2-yl)azetidine-3-thiol hydrochloride (**10**). The compound (**2**) and various bromides were heated to furnish 3-bromoazetidine derivatives (**12b,c,e,f**) and/or *N*,*N*-disubstituted 2,3-dibromopropylamines (**13a,c-f**). The reaction of **2** with benzoyl peroxide or *N*-bromosuccinimide gave each corresponding 1,3-disubustituted azetidine derivative (**14** or **15**).

1-Azabicyclo[1.1.0]butane (**2**) has proved to be the unique molecule bearing the highly strained bicyclic structure[1] and is synthetically useful for the preparation of 3-monosubstituted or 1,3-disubstituted azetidines.[2,3] Recently, we have disclosed an efficient synthetic method of **2** starting from 2,3-dibromopropylamine hydrobromide (**1**) and its application to the syntheses of some 3-subustituted

†Dedicated to Prof. James P. Kutney on the occasion of his 70th birthday.

azetidines, 1-(1,3-thiazolin-2-yl)azetidine-3-thiol hydrochloride (**10**) which was exploited for the synthesis of a new oral 1β-methylcarbapenem antibiotic L-084,[2] and an energetic material 1,3,3-trinitroazetidine.[4] We describe here the detailed results of synthesis of various azetidine derivatives by employing 1-azabicyclo[1.1.0]butane (**2**).

A THF solution of **2**, obtained from treatment of **1** with *n*-BuLi at -78 ℃ in THF followed by codistillatin with THF,[2,4] was allowed to react with several reagents E-Nu at room temperature to give the corresponding 3-monosubstituted and 1,3-disubstituted azetidine derivatives (**3**-**7**) in 30-77% yields, as shown in Scheme 1 and Table 1. Specifically, 3-hydroxyazetidine hydrochloride (**7**),[5] useful for the syntheses of charamin[6]

Scheme 1.

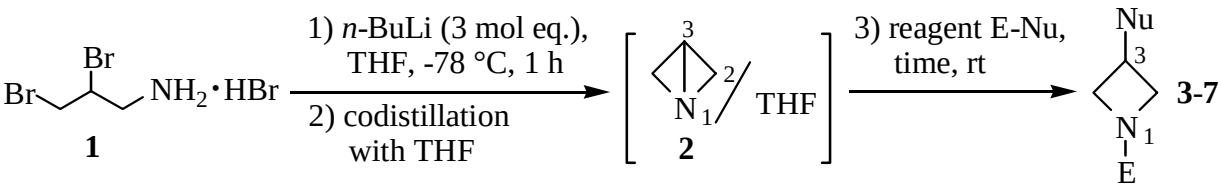


Table 1. Reaction of 1-Azabicyclo[1.1.0]butane (**2**) with Various Reagents

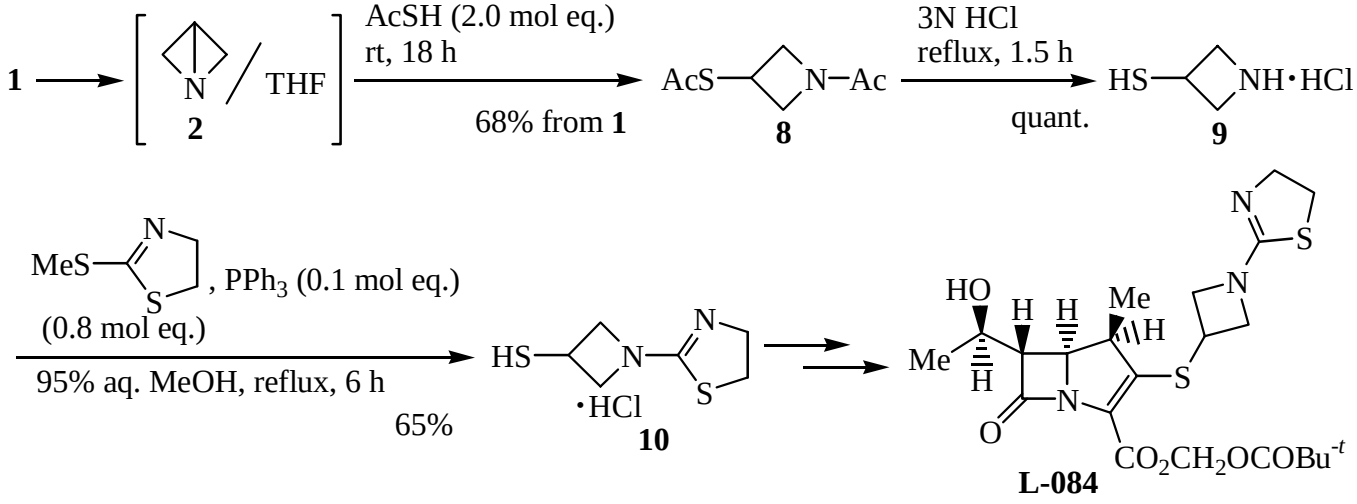
entry	reagent (mol eq.)	time (h)	product	yield (%)[a)]
1	HCl (3.0) / EtOH	0.5	Cl—NH·HCl **3**	70
2	48% HBr (3.0)	18	Br—NH·HBr **4**	60
3	$ClCO_2Et$ (1.3)	1	Cl—NCO_2Et **5**	77
4	Ts_2O (1.3)	2	TsO—NTs **6**	30
5	HCO_2H (1.2) 2.7N HCl / MeOH	18 20	HO—NH·HCl **7**	61
6	Ac_2O (1.3) 3N HCl[b)]	10 3	HO—NH·HCl **7**	62

[a)]Isolation yield from **1** [b)]Under reflux

and quinolone antibiotics,[7] was readily prepared by two kinds of procedures as follows. Treatment of **2** with formic acid or acetic anhydride followed by acidic hydrolysis employing 2.7N HCl in MeOH at

room temperature or 3N HCl under reflux afforded **7** in *ca.* 60% yield. Versatile 3-bromoazetidine hydrobromide (**4**), which can be exploited to synthesize various azetidine derivatives *via* suitable nucleophilic reactions, was also obtained by the reaction of **2** with 48% HBr. Any azilidine derivative due to the nucleophilic reaction at the C2 position, has never been furnished through all of the reactions. All the desirable reactions may proceed according to a concerted manner, in which an electrophilic group (E) initiates attacking the N1 position of the strained molecule (**2**) followed by cleavage of the highly strained N1-C3 σ-bond and then a nucleophilic group (Nu) reacts with the cationic C3 position. As a particular application of this azetidine synthesis, 2-(3-mercaptoazetidin-1-yl)-1,3-thiazoline hydrocloride (**10**), useful for the pendant moiety of new oral 1β-methylcarbapenem antibiotic L-084,[2] was successfully synthesized as shown in Scheme 2. Namely, conversion of **1** to 1-acetyl-3-acetylthioazetidine (**8**) (68% yield from **1**) was carried out by treatment of **2** with thiolacetic acid. Compound (**8**) was quantitatively hydrolyzed with 3N HCl under reflux to give azetidine-3-thiol hydrochloride (**9**). Reaction of **9** with 2-methylthio-1,3-thiazoline in the presence of catalytic triphenylphosphine in 95% aqueous MeOH under reflux afforded the desired compound (**10**) in 65% yield. Because chromatographic purification through the reaction pathway (**1**→**10**) is unnecessary, this synthetic method is remarkably efficient for the large-scale synthesis of **10**.

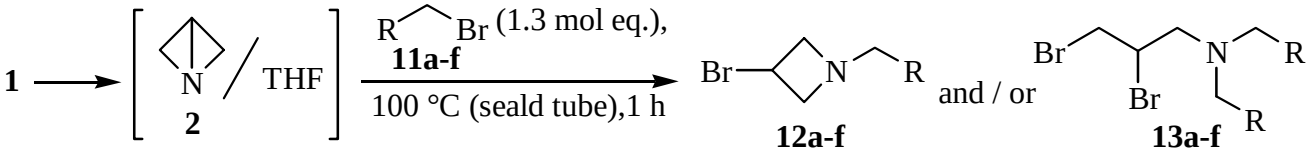
Scheme 2.



Subsequently, reactions of **2** with various bromides were examined (Scheme 3). All results are summarized in Table 2. Since the reactions did not proceed under the same conditions described in Scheme 1 and Table 1, we attempted them in a sealed tube at 100 ℃.

Thus, 3-bromoazetidine derivatives (**12b**,**c**,**e**,**f**) and/or *N*,*N*-disubstituted 2,3-dibromopropylamines (**13a**,**c-f**) were obtained in various yields, respectively. The former (**12**) should be produced in the similar manner to the case of **3-7** in Scheme 1, while the latter (**13**) seemed to be caused by nucleophilic

Scheme 3.



a : R = Ph, **b** : R = CN, **c** : R = CO_2Et, **d** : R = COPh, **e** : R = $CH=CH_2$, **f** : R = C≡R

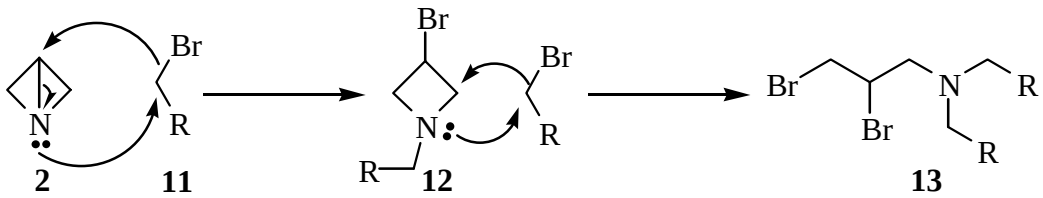
Table 2. Reaction of **2** with Bromides

entry	bromide (**11**)	product (**12**), yield (%)[a)]	product (**13**), yield (%)[a)]
1	**11a**	**12a**, N.D.[b)]	**13a**, 42
2	**11b**	**12b**, 45	**13b**, N.D.[b)]
3	**11c**	**12c**, 8	**13c**, 25
4	**11d**	**12d**, N.D.[b)]	**13d**, 40
5	**11e**	**12e**, 10	**13e**, 6
6	**11f**	**12f**, 6	**13f**, 19

[a)]Isolation yield from **1** [b)]Not detected.

attack of the N1 atom of **12** to the positive methylene carbon atom of the bromides releasing Br^- followed by N1-C2 cleavage with attack of the resultant Br^- to the C2 atom, as shown in Scheme 4. However, rational explanation for the product ratio **12**/**13** in each reaction is difficult. The reaction of **2** with bromides should be the first example.

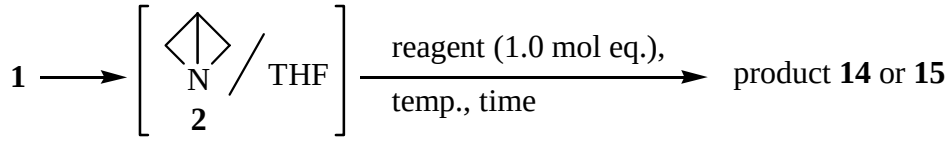
Scheme 4.

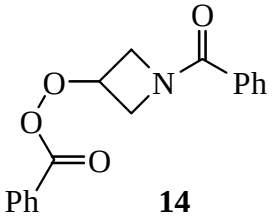
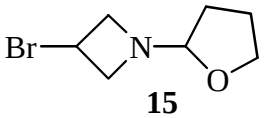


Finally, we attempted some reactions of **2** with radical initiators such as benzoyl peroxide (BPO), 2,2´-azobisisobutyronitrile (AIBN) and *N*-bromosuccinimide (NBS), as shown in Table 3. In the

reaction with BPO, 1-benzoyl-3-benzoylperoxyazetidine (**14**) was produced *via* the common ionic reaction, as described above. The reaction with NBS gave a radical reaction product (**15**) in a very low yield. On the other hand, the reaction with AIBN under heating resulted in production of inseparable mixture.

Table 3. Reaction of **2** with Radical Initiators and NBS



entry	reagent	temp.	time (h)	product	yield[a] (%)
1	BPO	rt	17	 **14**	11
2	AIBN	100 °C[b]	4	inseparable products	—
3	NBS	rt	20	 **15**	3

[a]Isolation yield from **1** [b]In a seald tube

In conclusion, we demonstrated the versatility of 1-azabicyclo[1.1.0]butane (**2**) for the synthesis of various 3-monosubstituted and 1,3-disubstituted azetidine derivatives (**3**-**9**, **12b**,**c**,**e**,**f**, **14** and **15**) and an efficient synthesis of the compound (**10**) useful for the 1β-methylcarbapenem antibiotic L-084.

ACKNOWLEDGEMENT

This work was supported by the Grants-in-Aid for Scientific Research on Priority Areas (A)(2)(No.13029085) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan and for Scientific Research (B)(2)(No. 12470482) from Japan Society for the Promotion of Science.

EXPERIMENTAL

All melting points were measured using a Yanagimoto apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1720 infrared Fourier transform spectrophotometer. ^{1}H NMR (200 MHz, 400 MHz) and ^{13}C NMR (100 MHz) spectra were taken on a JEOL JNM-FX 200 or JEOL JNM-GSX 400 spectrometer with tetramethylsilane as an internal standard, and chemical shifts are recorded in δ values.

HR-MS (EI) was measured on a JEOL JMS SX-102A mass spectrometer using a direct inlet system. Combustion analyses were performed by a Yanagimoto CHN Corder. Column chromatography was performed on Katayama silica gel (60K070 70-230 mesh) or Wakogel C-200 (75-150 ⌈m). Preparative TLC was carried out using 0.5 mm E. Merck silica gel (60 F_{254}).

THF solution of 1-azabicyclo[1.1.0]butane (2)[2,4]

A hexane solution of *n*-BuLi (50.4 mmol) was added dropwise to a suspension of **1** (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 reaction was quenched with 50% KOH and distilled at 80 °C. The resulting THF solution was dried over K_2CO_3 and filtered. The filtrate was adjusted to the 100 mL volume with THF. This THF solution of **2** was used the following reactions. The ^{1}H NMR and ^{13}C NMR spectral data were recorded on the earlier paper.[1a,2]

3-Chloroazetidine hydrochloride (3)

To a THF solution of **2** (40 mL) was added dropwise a saturated solution of HCl in EtOH (5 mL) at 0 °C, and the mixture was stirred at rt for 30 min. The reaction mixture was evaporated *in vacuo* to give a residue, which was washed with $CHCl_3$ (50 mL) and crystallized from MeOH-AcOEt to give compound (**3**) (864 mg, 70% yield from **1**) as colorless needles. mp 136 °C; ^{1}H NMR (200 MHz, CD_3OD) δ 4.16 (2H, dd, *J* = 5.3 and 12.7 Hz), 4.62 (2H, dd, *J* = 7.1 and 12.7 Hz), 4.8-5.0 (1H, m); IR (KBr) 3014, 2878, 2800, 2649, 1447, 1356, 1276, 1021 cm^{-1}; HR-MS (EI): Calcd for C_3H_6NCl: 91.0189, Found *m*/*z*: 91.0183 (M^+); Anal. Calcd for $C_3H_7NCl_2$: C, 28.15; H, 5.51; N, 10.94. Found: C, 28.08; H, 5.38; N, 10.99.

3-Bromoazetidine hydrobromide (4)

To a THF solution of **2** (25 mL) was added dropwise a 48% HBr (1.8 mL) at 0 °C, and the mixture was stirred at rt for 30 min. The reaction mixture was evaporated *in vacuo* to give a residue, which was washed with MeCN (50 mL) and crystallized from MeOH - AcOEt to give compound (**4**) (538 mg, 60% yield from **1**) as colorless needles. mp 119 °C; ^{1}H NMR (200 MHz, CD_3OD) δ 4.26 (2H, dd, *J* = 5.1 and 12.4 Hz), 4.74 (2H, dd, *J* = 7.1 and 12.4 Hz), 4.8-5.0 (1H, m); IR (KBr) 3003, 2881, 2630, 2428, 1441, 1338, 1269, 1229 cm^{-1}; HR-MS (EI): Calcd for C_3H_6NBr: 134.9684, Found *m*/*z*: 134.9684 (M^+); Anal. Calcd for $C_3H_7NBr_2$: C, 16.61; H, 3.25; N, 6.46. Found: C, 16.60; H, 3.21; N, 6.47.

1-Carboethoxy-3-chloroazetidine (5)

To a THF solution of **2** (20 mL) was added dropwise ethylchloroformate (0.44 mL, 4.6 mmol) and the mixture was stirred at rt for 1 h. The reaction mixture was evaporated *in vacuo*, and the residue was purified by column chromatography on a silica gel column with *n*-hexane - AcOEt (5 : 1). Compound (**5**) (419 mg, 77% yield from **1**) was obtained as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (3H, t, *J* = 7.1 Hz), 4.0-4.2 (4H, m), 4.46 (2H, q, *J* = 7.1 Hz), 4.4-4.6 (1H, m); IR (neat) 2982, 1708, 1421, 1381, 1177, 1136, 1024, 771 cm^{-1}; HR-MS (EI): Calcd for $C_6H_{10}NO_2Cl$: 163.0400, Found *m*/*z*: 163.0416 (M^+).

1-Tosyl-3-tosyloxyazetidine (6)

To a THF solution of **2** (20 mL) was added *p*-toluenesulfonic anhydride (1.50 g, 4.6 mmol) at 0 °C, and the mixture was stirred at rt for 15 min. The reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography on a silica gel column with *n*-hexane - AcOEt (2 : 1) to give compound (**6**) (391 mg, 31% yield from **1**) as colorless needles from *n*-hexane - AcOEt. mp 137 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.45 (6H, s), 3.68 (2H, dd, *J* = 5.1 and 9.8 Hz), 3.95 (2H, dd, *J* = 6.6 and 9.8 Hz), 4.7-4.9 (1H, m), 7.34 (2H, d, *J* = 8.3 Hz), 7.37 (2H, d, *J* = 8.3 Hz), 7.67 (2H, d, *J* = 8.3 Hz), 7.68 (2H, d, *J* = 8.3 Hz); IR (KBr) 2925, 1597, 1467, 1380, 1344, 1178, 1000, 672 cm^{-1}; HR-MS (EI): Calcd for $C_{17}H_{19}NO_5S_2$: 382.0783, Found *m*/*z*: 382.0773 (M^+). Anal. Calcd for $C_{17}H_{19}NO_5S_2$: C, 53.53; H, 5.02; N, 3.67. Found: C, 53.14; H, 5.06; N, 3.55.

3-Hydroxyazetidine hydrochloride (7)

(Method 1) : To a THF solution of **2** (20 mL) was added dropwise formic acid (0.21 mL, 4.6 mmol) at -40 °C, and the mixture was stirred at rt for 10 h. After the reaction mixture was evaporated *in vacuo,* the resultant residue was disolved in 2.7N HCl - MeOH solution (5 mL) and then the mixture was stirred at rt for 18 h. The reaction mixture was washed with ether, and evaporated under reduced pressure. The residue was crystallized from MeOH - acetone to give the known compound (**7**) (294 mg, 58% yield from **1**) as colorless needles. mp 88-90 °C (lit.,[5b] mp 91-92 °C).

(Method 2) : To a THF solution of **2** (20 mL) was added dropwise acetic anhydride (0.5 mL, 5.3 mmol) at -40 °C, and the mixture was stirred at rt for 10 h. After the reaction mixture was evaporated *in vacuo*, the residue was refluxed in 3N HCl (8 mL) for 3 h. The solid reaction mixture was washed with ether, and evaporated under reduced pressure. The solid residue was crystallized from MeOH - acetone to give the known compound (**7**) (312 mg, 62% yield from **1**) as colorless needles.

1-Acetyl-3-acetylthioazetidine (8)

To a THF solution of **2** (200 mL) was added dropwise a THF (12 mL) solution of thiolacetic acid (7.91 mL, 111 mmol) at –4 °C under argon, and the mixture was stirred at rt for 18 h. Then, the reaction mixture was evaporated *in vacuo* to give an oily residue, which was dissolved in AcOEt. The AcOEt solution was washed with 0.3N HCl, sat. $NaHCO_3$, brine, and dried over $MgSO_4$. After filtration, the filtrate was evaporated *in vacuo* to give an oily residue. The residue was purified by column chromatography on silica gel with CH_2Cl_2 to give compound (**8**) (6.02 g, 63%) as a colorless oil. ^{1}H NMR (200 Mz, $CDCl_3$) δ 1.86 (3H, s), 2.36 (3H, s), 4.8 - 5.7 (5H, m); IR (neat) 1691, 1655, 1509, 1420, 1357, 1136, 949, 773 cm^{-1}; HR-MS (EI): Calcd for $C_7H_{11}NO_2S$ 173.0511, Found *m/z*: 173.0509 (M^+).

3-Mercaptoazetidine hydrochloride (9)

Compound (**8**) (5.14 g, 29.7 mmol) was dissolved in 3N HCl (49 mL), and the acidic solution was refluxed for 3 h. Then, the reaction mixture was repeatedly washed with AcOEt, and evaporated *in vacuo* to give compound (**9**) (3.77 g, quantitative yield) as colorless oil. ^{1}H NMR (200 Mz, $CDCl_3$) δ 3.9 – 4.2

(3H, m), 4.2 – 4.3 (2H, m); IR (KBr) 3856, 2999, 2619, 1476, 1309 cm^{-1}; HR-MS (EI): Calcd for C_3H_7NS 90.0377, Found *m/z*: 90.0387 ($(M+1)^+$).

2-(3-Mercaptoazetidin-1-yl)-1,3-thiazoline hydrochloride (10)

Compound (**9**) (1.759 g, 14 mmol), 2-methylthio-1,3-thiazoline (1.492 g, 11.2 mmol), and PPh_3 (0.368 g, 1.4 mmol) were dissolved in 95% aqueous MeOH solution (20 mL), and the mixture was refluxed for 6 h. The reaction mixture was evaporated *in vacuo* to afford a solid residue. The residue was crystallized from MeCN (1.9 mL) - acetone (15 mL) to give compound (**10**) (2.114 g, 65%) as colorless needles. mp 125 – 127 °C (decomp); ^{1}H NMR (200 Mz, $CDCl_3$) δ 2.60 (1H, dd, *J* = 8.6 Hz), 3.60 (2H, t, *J* = 7.3 Hz), 3.9 - 4.2 (2H, m), 4.13 (2H, t, *J* = 7.3 Hz), 5.1 - 5.2 (2H, m), 12.11 (1H, brs); IR (KBr) 2952, 2751, 1641, 1455, 1445, 1133 cm^{-1}; HRMS (EI): Calcd for $C_6H_{10}N_2S_2$ 174.0285, Found *m/z*: 175.0372 ($(M+1)^+$); Anal. Calcd for $C_6H_{11}N_2ClS_2$: C, 34.19; H, 5.26; N, 13.29. Found : C, 34.06; H, 5.20; N, 13.21.

General procedure for the reaction with bromides

To a THF solution of **2** (20 mL) was added an indicated amount of bromide, and the mixture in a sealed tube was stirred at 100 °C for 1 h. The reaction mixture was evaporated *in vacuo*, and the residue was chromatographed on a preparative TLC plate.

2,3-Dibromo-1-(*N*,*N*-dibenzylamino)propane (13a)

Compound (**13a**) was prepared by using benzyl bromide (0.55 mL, 4.6 mmol) according to the general procedure. Preparative TLC was developed with *n*-hexane - AcOEt (9 : 1). 475 mg (42% yield from **1**); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.87 (1H, dd, *J* = 6.6 and 13.9 Hz), 3.19 (1H, dd, *J* = 7.1 and 13.9 Hz), 3.5-3.7 (6H, m), 3.9-4.1 (1H, m), 7.2-7.4 (10H, m); IR (neat) 2803, 2363, 1494, 1453, 1369, 1071, 1029, 747, 699 cm^{-1}; HR-MS (EI): Calcd for $C_{17}H_{19}NBr_2$: 394.9884, Found *m/z*: 394.9875 (M^+). Anal. Calcd for $C_{17}H_{19}NBr_2$: C, 51.65; H, 4.85; N, 3.55. Found: C, 51.63; H, 5.07; N, 3.77.

3-Bromo-1-cyanomethylazetidine (12b)

Compound (**12b**) was prepared by using bromoacetonitrile (0.32 mL, 4.6 mmol) according to the general procedure. Preparative TLC was developed with *n*-hexane - AcOEt (1 : 1). 260 mg (45% yield from **1**); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.51 (2H, s), 3.66 (2H, dd, *J* = 5.1 and 8.5 Hz), 3.99 (2H, dd, *J* = 8.5 and 8.8 Hz), 4.3-4.5 (1H, m); IR (neat) 2960, 2342, 1229, 867, 773, 669 cm^{-1}; HR-MS (EI): Calcd for $C_5H_7N_2Br$: 175.9772, Found *m/z*: 175.9762 (M^+).

Ethyl 2-(3-Bromoazetidin-1-yl)acetate (12c) and 2,3-Dibromo-1-[*N*,*N*-bis(ethoxycarbonylmethyl)-amino] propane (13c)

Compounds (**12c** and **13c**) were prepared by using ethyl bromoacetate (0.51 mL, 4.6 mmol) according to the general procedure. Preparative TLC was developed with *n*-hexane - AcOEt (5 : 1). **12c**: 63 mg (8% yield from **1**); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (3H, t, *J* = 7.1 Hz), 3.35 (2H, s), 3.56 (2H, dd, *J* = 6.4 and 8.6 Hz), 4.06 (2H, dd, *J* = 6.8 and 8.6 Hz), 4.16 (2H, q, *J* = 7.1 Hz), 4.4-4.6 (1H, m); IR (neat) 2980, 1742, 1379, 1193, 1031 cm^{-1}; HR-MS (EI): Calcd for $C_7H_{12}NO_2Br$: 223.0031, Found

m/*z*: 223.0037 (M^+). **13c**: 323 mg (25% yield from **1**); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (6H, t, *J* = 7.1 Hz), 3.30 (2H, d, *J* = 6.1 Hz), 3.65 (4H, s), 3.90 (1H, dd, *J* = 6.8 and 10.7 Hz), 4.02 (1H, dd, *J* = 4.2 and 10.7 Hz), 4.18 (4H, q, *J* = 7.1 Hz), 4.2-4.3 (1H, m); IR (neat) 2981, 1736, 1371, 1191, 1027, 879, 669, 402 cm^{-1}; HR-MS (EI): Calcd for $C_{11}H_{19}NO_4Br_2$: 390.9640, Found *m*/*z*: 390.9637 (M^+). Anal. Calcd for $C_{11}H_{19}NO_4Br_2$: C, 34.11; H, 4.95; N, 3.62. Found: C, 34.01; H, 4.90; N, 3.70.

2,3-Dibromo-1-[*N*,*N*-bis(phenylcarbonylmethyl)amino]propane (13d)

Compound (**13d**) was prepared by using 2-bromoacetophenone (916 mg, 4.6 mmol) according to the general procedure. Preparative TLC was developed with *n*-hexane - AcOEt (5 : 1). **13d**: 606 mg (40% yield from **1**); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.48 (2H, d, *J* = 5.9 Hz), 3.94 (1H, dd, *J* = 7.1 and 10.7 Hz), 4.07 (1H, dd, *J* = 4.2 and 10.7 Hz), 4.2-4.4 (1H, m), 4.52 (4H, s), 7.4-7.6 (6H, m), 7.93 (4H, d, *J* = 7.1 Hz); IR (neat) 3062, 2907, 1695, 1598, 1581, 1449, 1412, 1074, 957, 886, 689 cm^{-1}; HRMS (EI): Calcd for $C_{19}H_{19}NO_2Br_2$: 454.9742, Found *m*/*z*: 454.9729 (M^+).

3-Bromo-1-allylazetidine (12e) and 2,3-dibromo-1-(*N*,*N*-diallylamino)propane (13e)

Compounds (**12e** and **13e**) were prepared by using allyl bromide (0.38 mL, 4.6 mmol) according to the general procedure. Preparative TLC was developed with *n*-hexane - AcOEt (3 : 1). **12e**: 59 mg (10% yield from **1**); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.14 (2H, d, *J* = 6.1 Hz), 3.40 (2H, dd, *J* = 6.4 and 9.1 Hz), 3.87 (2H, dd, *J* = 7.6 and 9.1 Hz), 4.4-4.6 (1H, m), 5.11 (1H, d, *J* = 9.8 Hz), 5.18 (1H, d, *J* = 15.6 Hz), 5.6-5.9 (1H, m); IR (neat) 1655, 1639, 1364, 922, 773 cm^{-1}; HR-MS (EI): Calcd for $C_6H_{10}NBr$: 174.9997, Found *m*/*z*: 174.9980 (M^+). **13e**: 60 mg (6% yield from **1**); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.85 (1H, dd, *J* = 6.6 and 14.2 Hz), 3.02 (1H, dd, *J* = 7.1 and 14.2 Hz), 3.18 (4H, d, *J* = 6.4 Hz), 3.79 (1H, dd, *J* = 6.4 and 10.7 Hz), 3.90 (1H, dd, *J* = 5.9 and 10.7 Hz), 4.1-4.3 (1H, m), 5.19 (2H, d, *J* = 18.0 Hz), 5.22 (2H, d, *J* = 9.0 Hz), 5.7-6.0 (2H, m); IR (neat) 2814, 1643, 1450, 1419, 1256, 995, 923, 669 cm^{-1}; HR-MS (EI): Calcd for $C_9H_{15}NBr_2$: 296.9551, Found *m*/*z*: 296.9519 (M^+).

3-Bromo-1-(1-propyn-3-yl)azetidine (12f) and 2,3-Dibromo-1-[*N*,*N*-bis(1-propyn-3-yl)amino]propane (13f)

Compounds (**12f** and **13f**) were prepared by using propargyl bromide (0.34 mL, 4.6 mmol) according to the general procedure. TLC was developed with *n*-hexane - AcOEt (4 : 1). **12f**: 34 mg (6% yield from **1**); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.33 (1H,s), 3.33 (2H, s), 3.60 (2H, dd, *J* = 5.9 and 7.6 Hz), 4.06 (2H, dd, *J* = 6.8 and 7.6 Hz), 4.4-4.5 (1H, m); IR (neat) 3737, 3293, 2919, 2837, 2364, 1654, 1559, 1541, 1508, 1438 cm^{-1}; HR-MS (EI): Calcd for C_6H_8NBr: 172.9840, Found *m*/*z*: 172.9843 (M^+). **13f**: 183 mg (19% yield from **1**); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.26 (2H, t, *J* = 2.4 Hz), 3.00 (1H, dd, *J* = 6.6 and 14.4 Hz), 3.15 (1H, dd, *J* = 6.3 and 14.4 Hz), 3.53 (4H, d, *J* = 2.4 Hz), 3.80 (1H, dd, *J* = 6.8 and 10.5 Hz), 3.90 (1H, dd, *J* = 4.6 and 10.5 Hz), 4.1-4.3 (1H, m); IR (neat) 3294, 2926, 2359, 1436, 1330, 1128, 636 cm^{-1}; HR-MS (EI): Calcd for $C_9H_{11}NBr_2$: 292.9238, Found *m*/*z*: 292.9215 (M^+).

1-Benzoyl-3-benzoylperoxyazetidine (14)

To a THF solution of **2** (20 mL) was added benzoyl peroxide (2.23 mg, 9.2 mmol) at 0 °C, and the

mixture was stirred at rt for 15 h. The reaction mixture was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column with *n*-hexane - AcOEt (2 : 1). Compound (**14**) (300 mg, 11% yield from **1**) was obtained as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.36 (2H, dd, *J* = 3.4 and 10.7 Hz), 4.5-4.8 (2H, m), 5.4-5.6 (1H, m), 7.3-7.7 (8H, m), 8.05 (2H, d, *J* = 7.1 Hz); IR (neat) 1723, 1635, 1577, 1451, 1417, 1274, 1120, 1072 cm^{-1}; HR-MS (EI): Calcd for $C_{17}H_{15}NO_4$: 297.1001, Found *m*/*z*: 297.0988 (M^+).

3-Bromo-1-(tetrahydrofuran-2-yl)azetidine (15)

To a THF solution of **2** (20 mL) was added *N*-bromosuccinimide (818 mg, 4.6 mmol), and the mixture in sealed tube was stirred at 100 °C for 1 h. The reaction mixture was evaporated *in vacuo*, and the residue was chromatographed on a preparative TLC plate with *n*-hexane - AcOEt (2 : 1). Compound (**15**) (27 mg, 3% yield from **1**) was obtained as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.4-1.6 (1H, m), 1.9-2.0 (3H, m), 3.65 (2H, dd, *J* = 5.3 and 13.4 Hz), 3.9-4.0 (4H, m), 4.4-4.6 (2H, m); IR (neat) 2948, 2865, 1460, 1377, 1239, 1036, 839 cm^{-1}; HR-MS (EI): Calcd for $C_7H_{12}NOBr$: 207.0082, Found *m*/*z*: 207.0130 (M^+).

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