Effective Ring-Opening Reaction of Aziridines with Trimethylsilyl Compounds: A Facile Access to β-Amino Acids and 1,2-Diamine Derivatives

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Ring-opening reactions of aziridines with trimethylsilyl compounds triggered by tetrabutylammonium fluoride give the corresponding products regioselectively in excellent yield. It provides a facile and efficient procedure for the ring-opening reactions of aziridines and affords a practical access to the synthesis of cyano-, azido-, or chloroamines because of its efficiency and simplicity. The products are easily transformed to vicinal diamines or β-amino acids.

Introduction

Organosilicon compounds are among the most widely used reagents in organic synthesis because of their versatile reactivity and high tolerance for other functional groups. Sakurai and co-workers[1a] described the allylation of carbonyl compounds with allylsilane under Lewis acid condition or in the presence of catalytic quantities of fluoride ions a reaction now known as Sakurai−Hosomi reaction. The reaction has been extensively applied in organic synthesis[1b−g] and has been extended to the allylation of imines.[2] There is significant current interest in the synthesis and reaction of aziridines and their N-activated analogues.[3] Due to their very high reactivity and ability to function as carbon electrophiles, aziridine derivatives are versatile intermediates for the synthesis of biologically important compounds. A number of ring-opening reactions of activated and unactivated aziridines have been reported,[4,5] including reactions of aziridines with trimethylsilyl compounds in the presence of transition metal-based catalysts. For example, Yeung and co-workers[6] reported the azidolysis of *N*-tosylaziridines with trimethylsilyl azide in the presence of a chromium complex. However, the results were not satisfactory (regioselectivity, 1:1−40:1; yield, 18−97%), and the reaction time was too long (2−9 days). Very recently, Lectka and co-workers[7] reported the azidolysis of *N*-benzoylaziridine catalyzed by transition-metal-based complexes causes rearrangement to oxazoline. Ring opening of aziridines in the presence of 2 equiv of trimethylsilyl cyanide (TMSCN) and 25 mol % of lanthanum tricyanide at 65 °C was also reported,[8,9] but the catalyst was not easy to prepare. Ohno and co-workers[10] also reported the ring-opening of *N*-(4-toluenesulfonyl)propyleneimine with acetone cyanohydrin using 10 mol % of La(O*i*-Pr)$_3$ at 50 °C for 4 h to give the corresponding *N*-(4-toluenesulfonyl)-amino nitrile in 74% yield.

Recently, we have shown that fluoride ion is an effective trigger of the reaction of allyltrimethylsilane with imines, leading to homoallylamines in high yield.[2] As part of a program aimed at the synthesis of epoxides and aziridines and their applications in organic synthesis,[11] we have studied the ring-opening reactions of these small heterocyclic compounds.[12] We have found that the use of fluoride to trigger the reaction of an organosilica

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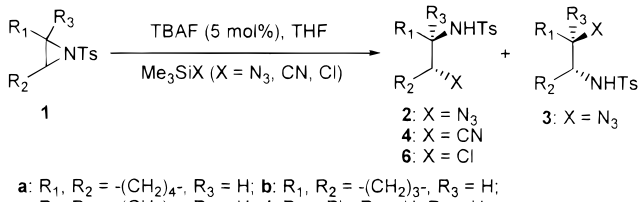
Scheme 1



a: R_1, R_2 = -$(CH_2)_4$-, R_3 = H; **b**: R_1, R_2 = -$(CH_2)_3$-, R_3 = H; **c**: R_1, R_2 = -$(CH_2)_6$-, R_3 = H; **d**: R_1 = Ph, R_2 = H, R_3 = H; **e**: R_1 = ^{n}Bu, R_2 = H, R_3 = H; **f**: R_1 = $^n C_6H_{13}$, R_2 = H, R_3 = H; **g**: R_1 = H, R_2 = H, R_3 = H; **h**: R_1, R_2 = -$(CH_2)_4$-, R_3 = CH_3.

Table 1. Ring-Opening Reactions of *N*-tosylaziridines with TMSX (X = N_3, CN, Cl) Triggered by TBAF[a]

entry	aziridine	TMSX	time (h)	**2**/**3**[b]	yield[c] (%)
1	**1a**	$TMSN_3$	4(8)[d]		>99 (98)[d] (**2a**)
2	**1b**	$TMSN_3$	12(8)[e]		83 (96)[e] (**2b**)
3	**1c**	$TMSN_3$	12		
4	**1d**	$TMSN_3$	4(2)[e]	36/64 (42/58)[e]	90 (>99)[e] (**2d**/**3d**)
5	**1e**	$TMSN_3$	6(4)[e]	>99/1 (>99/1)[e]	97 (97)[e] (**2e**)
6	**1f**	$TMSN_3$	4	>99/1	99 (**2f**)
7[d]	**1g**	$TMSN_3$	12		95 (**2g**)
8	**1h**	$TMSN_3$	4	>99/1	60 (**2h**)
9	**1a**	TMSCN	0.5		95 (**4a**)
10	**1b**	TMSCN	5		>99 (**4b**)
11	**1c**	TMSCN	24		
12	**1d**	TMSCN	0.6		>99 (**4d**)
13	**1e**	TMSCN	0.3		>99 (**4e**)
14	**1f**	TMSCN	2		82 (**4f**)
15[d]	**1g**	TMSCN	10		91 (**4g**)
16	**1h**	TMSCN	8		79 (**4h**)
17	**1a**	TMSCl	0.1		97 (**6a**)
18	**1b**	TMSCl	0.1		94 (**6b**)
19[d]	**1g**	TMSCl	12		99 (**6g**)

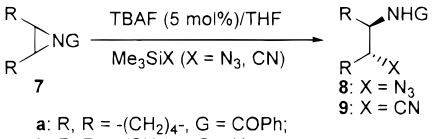
[a] Reaction conditions: aziridine (0.25 mmol), TMSX (0.25 mmol), and TBAF (13 μL, 1.0 M in THF) at 40 °C. [b] The ratio is determined by ^{1}H NMR (300 MHz). [c] Isolated yield based on *N*-tosylaziridine. [d] The reaction was performed at room temperature. [e] The reaction was carried out in the presence of 4A molecular sieves.

reagent with electron-deficient substrates was also effective in the ring-opening reaction of aziridines with trimethylsilyl compounds. In the present paper, we report that fluoride ion in the form of tetrabutylammonium fluoride (TBAF) can trigger the reaction of aziridines with trimethylsilyl azide, trimethylsilyl cyanide, and trimethylsilyl chloride.

Results and Discussion

Ring-Opening Reactions of Aziridines by Using Fluoride as a Trigger. In the presence of a catalytic amount of TBAF, the reaction of aziridines **1** with trimethylsilyl compounds gives rise to the corresponding ring-opening products **2** and **3** in high yields and selectivities (Scheme 1). As may be seen in Table 1, a small amount of TBAF (5mol % relative to the silyl compound) was sufficient to initiate cleavage. Reactions occurred under mild conditions and were complete in 0.5−12 h. Yields were almost quantitative except in the case of **1c** (entries 3 and 11). No reaction took place in the absence of TBAF, and the increase in the amount of TBAF markedly reduced the reaction time. With 5 mol % of TBAF the reaction was complete in 4−12 h at 40 °C when

Scheme 2



a: R, R = -$(CH_2)_4$-, G = COPh; **b**: R, R = -$(CH_2)_4$-, G = H; **c**: R, R = -$(CH_2)_4$-, G = Bn; **d**: R, R = -$(CH_2)_3$-, G = Boc.

$TMSN_3$ was used as reagent, whereas the reaction time was reduced to 1 h and yield was almost quantitative when the amount of TBAF was increased to 20 mol % (data not shown).

In some cases, the addition of molecular sieves to the reaction mixture raised the yields (entries 2, 4, and 5) and enhanced the reaction rate, but did not improve regioselectivity (entry 4). Although the reaction of styrene *N*-tosylaziridine **1d** with trimethylsilyl azide afforded the 1- and 2- azido products with a selectivity of 58:42 (entry 4), azidolysis of **1e**, **1f**, and **1h** provided the 1- and 2-azido products with a ratio of >99:1 (entries 5, 6, and 8). When TMSCN was used as the nucleophile, as previously observed in common metal salt-promoted reactions,[12] the reactions were completely *anti* stereoselective, and in the case of unsymmetrically substituted aziridines, completely regioselective with the attack of nucleophile on the less substituted aziridine carbon even in the case of **1d** (entry 12). Although the TBAF catalyzed ring-opening reactions were quite efficient for mono- and disubstituted aziridines, the reaction of trisubstituted aziridine was sluggish and the yield was decreased. For example, when **1h** was the substrate in the reaction with TMSCN, the yield of product was 79% after 8 h (entry 16), which is much slower as compared with **1a** (95% yield, reaction time: 0.5 h) (entry 9). However, when **1g** was used as the substrate (entries 7, 15, and 19), the reaction was carried out at room temperature because the substrate was unstable on heating. A variety of solvents, such as CH_3CN, toluene, Et_2O, and CH_2Cl_2, are suitable for this reaction. We also found that the reaction of *N*-tosylaziridine with trimethylsilyl chloride in the presence of TBAF (5 mol %) proceeded smoothly and gave the *trans*-1-chloro-2-amino compounds **6** in essentially quantitative yields (entries 17, 18, and 19). However, the reaction of *N*-tosylaziridine with allyltrimethylsilane failed to give the corresponding product.

We also found that the group attached on the nitrogen atom is very important. To examine the effect of electron-withdrawing and electron-donating groups, we conducted the experiments depicted in Scheme 2 and found that electron-withdrawing substituents were necessary. For example, when **7b** or **7c** was used as the substrates, there was no reaction even after 24 h at 40 °C (Table 2, entries 3−6). Electron-withdrawing groups on the aziridine nitrogen are expected to stabilize the leaving group during nucleophilic attack. The *N*-Boc-aziridine derivative **7d** likewise failed to yield the expected product, but instead afforded only a small amount of an unknown byproduct (entries 7, 8).

Studies on the Mechanism of the Ring Opening Reaction. On studying the mechanism of Sakurai−Hosomi reaction, we found that it was a TBAF-triggered process and that the intermediate alkoxide or amide served as a base to cleave the TMS-allyl bond.[2] Does TBAF play a similar role in this ring opening reaction of aziridine with trimethylsilyl compounds? The following

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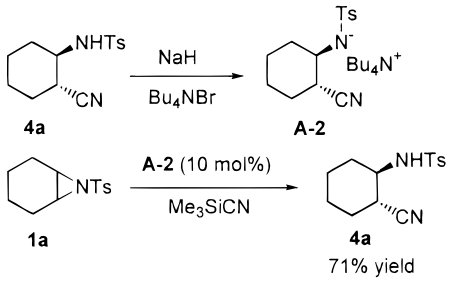
Table 2. Ring-Opening Reactions of Aziridines Attached with Various Groups on Nitrogen Atom with $TMSN_3$ and TMSCN Triggered by TBAF[a]

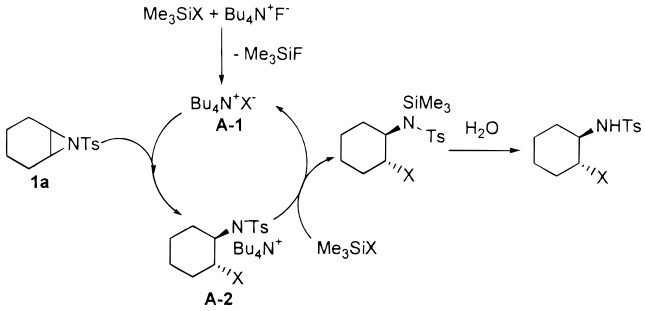
entry	aziridine	TMSX	time (h)	yield[b] (%)
1	**7a**	$TMSN_3$	8	82 (**8a**)
2	**7a**	TMSCN	12	88 (**9a**)
3	**7b**	$TMSN_3$	24	
4	**7b**	TMSCN	24	
5	**7c**	$TMSN_3$	24	
6	**7c**	TMSCN	24	
7	**7d**	$TMSN_3$	24	*c*
8	**7d**	TMSCN	24	*c*

[a] Reaction conditions: aziridine 0.25 mmol, TMSX 0.25 mmol, and TBAF (13 μL, 1.0 M in THF) at 40 °C. [b] Isolated yield based on aziridine. [c] Small amout of byproduct whose structure was not determined was obtained.

Scheme 3



Scheme 4



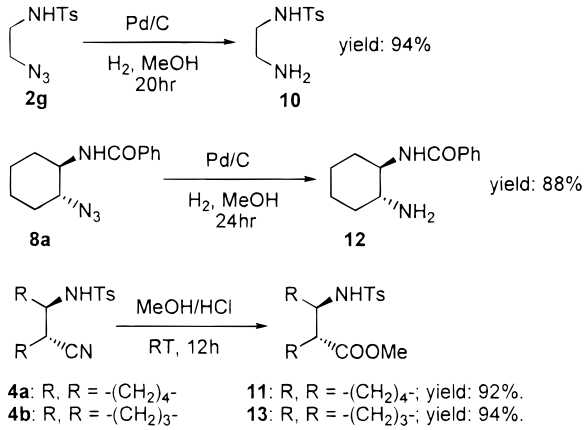
reaction (Scheme 3) showed us that the intermediate amide is also basic enough to cleave the TMS-X bond.

When **4a** was deprotonated with NaH in the presence of tetrabutylammonium bromide, the tetrabutylammonium salt **A-2** was obtained in good yield. When **A-2** was used to catalyzed the ring-opening of **1a** in the absence of fluoride ion, **4a** was obtained in good yield, suggesting that fluoride ion merely acted as an initiator in this reaction. Thus, we propose that this cleavage of aziridines likewise occurs via a mechanism analogous to that of the Sakurai−Hosomi reaction,[2] as represented in Scheme 4.

According to this mechanism, the interaction of the trimethylsilyl compounds and fluoride ion leads to the evolution of Me_3SiF and the species **A-1**, whereupon **A-1** reacts with the aziridine to afford **A-2**. The latter then reacts again with the trimethylsilyl compound to regenerate **A-1** and allow the catalytic cycle to be completed.

Based on the fact that Si−F, Si−O, Si−N, and Si−Cl bonds are stronger than Si−C bonds,[1h] the reaction would be expected to occur readily in the presence of chloride ion. In agreement with this expectation, when the reaction of **1a** with trimethylsilyl cyanide was performed with tetrabutylammonium chloride (20 mol %) instead of TBAF, **4a** was obtained in 85% yield after 48h at 40 °C. However, no reaction occurred when tetrabutylammonium chloride was used to catalyze the reaction of allyltrimethylsilane or TMSCN with an aldehyde or imine, suggesting that the substrate is as important as the catalyst in this system. Furthermore, we found that the cation also plays an important role in the reaction. For example, LiF, KF, LiCl, or NaCl (20 mol %) could not trigger the reaction of **1a** with TMSCN after 48 h, even in the presence of 18-crown-6 when KF was used. It seems that tetrabutylammonium cation is necessary in this reaction system.

Scheme 5



These ring-opening reaction products are useful synthetic intermediates in organic synthesis. They can easily and conveniently be transformed to vicinal diamines or β-amino acids. For example, *N*-(2-azidoethyl)-4-methylbenzenesulfonamide **2g**, derived from **1g**, is easily converted to diamines **10** by hydrogenation.[13] Hydrolysis of the nitrile **4a** with saturated methanolic HCl at room temperature produces the tosyl-protected amino ester **11**[14] (Scheme 5).

In conclusion, we develop an efficient and convenient ring-opening reactions of aziridines with trimethylsilyl compounds. It provides a facile route to the synthesis of vicinal diamines and β-amino acids because of its efficiency and simplicity. The studies toward asymmetric ring-opening reactions are under investigated in our laboratory.

Experimental Section

General Method. All reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were treated prior to use according to the standard method. The commercially available reagents were used as received without further purification. Melting points are uncorrected. The aziridines were prepared according to the literature procedures.[15]

General Procedure. To a solution of *N*-tosylaziridine (0.25 mmol) in THF (3.0 mL) were added trimethylsilyl compound (0.25 mmol) and TBAF (13 μL, 1.0 M in THF). The mixture was stirred at 40 °C and monitored by TLC. After consumption of the starting material, CH_2Cl_2 was added. The mixture was filtered through a plug of silica with 20 mL of CH_2Cl_2 as eluent. Removal of solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatog-

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raphy using petroleum ether−AcOEt (5:1) as an eluent to give the corresponding product.

***N*-(2-Azidocyclohexyl)-4-methylbenzenesulfonamide (2a).**[6] Colorless liquid. IR (film): 3273, 2940, 2863, 2100, 1599 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 1.10−1.45 (m, 4H), 1.60−1.80 (m, 2H), 1.95−2.15 (m, 2H), 2.45 (s, 3H), 2.90−3.00 (m, 1H), 3.00−3.10 (m, 1H), 4.80 (bd, J = 5.92 Hz, 1H), 7.35 (d, J = 7.98 Hz, 2H), 7.80 (d, J = 8.06 Hz, 2H). EIMS (relative intensity): 295 (MH^+, 1), 252 (13), 210 (73), 155 (86), 111 (70), 91 (100). HRMS: for $C_{13}H_{18}NO_2S$ $(M - N_3)^+$ calcd 252.1058, found 252.1070.

***N*-(2-Azidocyclopentyl)-4-methylbenzenesulfonamide (2b).** Colorless liquid. IR (film): 3270, 2966, 2104 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 1.30−1.50 (m, 1H), 1.55−1.75 (m, 3H), 1.90−2.05 (m, 2H), 2.45 (s, 3H), 3.35−3.50 (m, 1H), 3.70−3.80 (m, 1H), 4.90 (bd, J = 6.56 Hz, 1H), 7.35 (d, J = 8.23 Hz, 2H), 7.80 (d, J = 8.26 Hz, 2H). EIMS (relative intensity): 371 ($M^+ + 91$, 3), 281 (MH^+, 1), 251 (11), 238 (35), 155 (57), 133 (62), 91 (100). HRMS: for $C_{12}H_{16}NO_2S$ $(M - N_3)^+$ calcd 238.0901, found 238.0897.

***N*-(2-Azido-1-phenylethyl)-4-methylbenzenesulfonamide (2d).**[6] Colorless liquid. IR (film): 3279, 2105, 1599 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 2.40 (s, 3H), 3.55 (d, J = 5.89 Hz, 2H), 4.42−4.52 (dd, J = 12.89, 5.95, 5.91 Hz, 1H), 5.20 (d, J = 7.13 Hz, 1H), 7.10−7.40 (m, 7H), 7.65 (d, J = 8.31 Hz, 2H). EIMS (relative intensity): 274 ($(M - N_3)^+$, 1.91), 260 (25), 184 (35), 155 (74), 91 (100). HRMS: for $C_{15}H_{16}NO_2S$ $(M - N_3)^+$ calcd 274.0952, found 274.0927.

***N*-(2-Azido-2-phenylethyl)-4-methylbenzenesulfonamide (3d).**[6] Colorless liquid. IR (film): 3279, 2105, 1599 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 2.45 (s, 3H), 3.05−3.15 (m, 1H), 3.18−3.30 (m, 1H), 4.55−4.65 (dd, J = 8.84, 5.12, 5.11 Hz, 1H), 4.75−4.90 (m, 1H), 7.10−7.40 (m, 7H), 7.80 (d, J = 8.31, 2H). EIMS (relative intensity): 274 ($(M-N_3)^+$, 1.91), 260 (25), 184 (35), 155 (74), 91 (100). HRMS: for $C_{15}H_{16}NO_2S$ $(M - N_3)^+$ calcd 274.0952, found 274.0927.

***N*-(2-Azidohexyl)-4-methylbenzenesulfonamide (2e).**[6] Colorless liquid. IR (film): 3279, 2104, 1599 cm^{-1}. ^1H NMR ($CDCl_3$ /TMS) δ (ppm): 0.80 (t, J = 7.03, 4.01 Hz, 3H), 1.00−1.30 (m, 4H), 1.35−1.55 (m, 2H), 2.40 (s, 3H), 3.25−3.40 (m, 3H), 4.75 (d, J = 7.68 Hz, 1H), 7.35 (d, J = 8.60 Hz, 2H), 7.80 (d, J = 8.51 Hz, 2H). EIMS (relative intensity): 240 ($(M-CH_2N_3)^+$, 33), 155 (57), 91 (100). HRMS: for $C_{12}H_{18}NO_2S$ $(M - CH_2N_3)^+$ calcd 240.1114, found 240.1086.

***N*-(2-Azidooctyl)-4-methylbenzenesulfonamide (2f).** Colorless liquid. IR (film): 3279, 2930, 2860, 2104, 1599 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 0.85 (t, J = 7.17, 6.72 Hz, 3H), 1.00−1.35 (m, 7H), 1.35−1.60 (m, 3H), 2.45 (s, 3H), 3.20−3.40 (m, 3H), 4.55 (d, J = 7.70 Hz, 1H), 7.35 (d, J = 7.99 Hz, 2H), 7.80 (d, J = 8.31 Hz, 2H). EIMS (relative intensity): 325 (MH^+, 6.26), 282 (12), 268 (100), 254 (13), 155 (39), 91 (45). HRMS: for $C_{15}H_{25}N_4O_2S$ (MH^+) calcd 325.1698, found 325.1717.

***N*-(2-Azidoethyl)-4-methylbenzenesulfonamide (2g).** White solid. Mp: 37−38 °C. IR (film): 3305, 3268, 2928, 2104, 1598 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 2.40 (s, 3H), 3.10 (q, J = 11.92, 6.13, 5.77 Hz, 2H), 3.40 (t, J = 5.99, 5.53 Hz, 2H), 5.10 (br, 1H), 7.35 (d, J = 7.91 Hz, 2H), 7.75 (d, J = 8.31 Hz, 2H). EIMS (relative intensity): 241 (MH^+, 31), 225 (2), 184 (52), 155 (94), 91 (100). Anal. Calcd for $C_9H_{12}N_4O_2S$: C, 44.99; H, 5.03; N, 23.32. Found: C, 44.90; H, 5.00; N, 23.44.

***N*-(2-Azido-1-methylcyclohexyl)-4-methylbenzenesulfonamide (2h).** White solid. Mp: 148−149 °C. IR (film): 3270, 2933, 2092, 1599 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 1.20−1.40 (m, 6H), 1.40−1.70 (m, 4H), 1.80−1.90 (m, 1H), 2.40 (s, 3H), 3.05−3.15 (m, 1H), 4.60 (bd, J = 7.98 Hz, 1H), 7.30 (d, J = 8.14 Hz, 2H), 7.80 (d, J = 8.29 Hz, 2H). EIMS (relative intensity): 398 ($((M - 1) + 91)^+$, 0.2), 307 ($(M - 1)^+$, 1), 266 (95), 210 (27), 155 (28), 125 (100), 91 (70). Anal. Calcd for $C_{14}H_{20}N_4O_2S$: C, 54.52; H, 6.54; N, 18.17. Found: C, 54.18; H, 6.58; N, 18.45.

***N*-(2-Cyanocyclohexyl)-4-methylbenzenesulfonamide (4a).**[8] White solid. Mp: 113−114 °C. IR (film): 3279, 2245, 1600 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 1.20−1.50 (m, 3H), 1.50−1.80 (m, 3H), 1.85−2.20 (m, 2H), 2.40 (s, 3H), 2.60−2.90 (m, 1H), 3.30−3.50 (m, 1H), 5.25 (d, J = 7.92 Hz, 1H), 7.35 (d, J = 8.06 Hz, 2H), 7.80 (d, J = 8.21 Hz, 2H). EIMS (relative intensity): 278 (M^+, 19), 210 (100), 155 (61), 91 (96). Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.43; H, 6.47; N, 10.07. Found: C, 60.55; H, 6.66; N, 9.99.

***N*-(2-Cyanocyclopentyl)-4-methylbenzenesulfonamide (4b).** White solid. Mp: 107−108 °C. IR (KBr): 3252, 2933, 2244, 1600 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 1.40−1.60 (m, 1H), 1.60−2.30 (m, 5H), 2.45 (s, 3H), 2.75−3.00 (m, 1H), 3.70−3.90 (m, 1H), 5.45 (d, J = 6.57 Hz, 1H), 7.35 (d, J = 8.03 Hz, 2H), 7.85 (d, J = 8.18 Hz, 2H). EIMS (relative intensity): 265 (MH^+, 13), 264 (M^+, 25), 237 (10), 210 (55), 155 (70), 91 (100). Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60. Found: C, 58.90; H, 6.09; N, 10.39.

***N*-(2-Cyano-1-phenylethyl)-4-methylbenzenesulfonamide (4d).**[8] White solid. Mp: 120−121 °C. IR (film): 3250, 2252, 1597 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 2.40 (s, 3H), 2.80−3.00 (m, 2H), 4.50−4.60 (m, 1H), 5.45 (d, J = 6.64 Hz, 1H), 7.10−7.50 (m, 7H), 7.70 (d, J = 8.12 Hz, 2H). EIMS (relative intensity): 301 (MH^+, 0.29), 260 (100), 155 (65), 91 (89). Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 64.00; H, 5.33; N, 9.33. Found: C, 64.02; H, 5.35; N, 9.45.

***N*-(2-Cyanohexyl)-4-methylbenzenesulfonamide (4e).**[8] White solid. Mp: 73−74 °C. IR (film): 3262, 2248, 1599 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 0.77 (t, J = 7.22, 6.78 Hz, 3H), 1.00−1.30 (m, 4H), 1.40−1.60 (m, 2H), 2.40 (s, 3H), 2.50−2.60 (m, 2H), 3.40−3.50 (m, 1H), 4.80 (d, J = 7.72 Hz, 1H), 7.30 (d, J = 7.95 Hz, 2H), 7.80 (d, J = 8.29 Hz, 2H). EIMS (relative intensity): 281 (MH^+, 8), 240 (83), 155 (100), 91 (88). Anal. Calcd for $C_{14}H_{20}N_2O_2S$: C, 60.00; H, 7.14; N, 10.00. Found: C, 60.04; H, 7.30; N, 9.84.

***N*-(2-Cyanooctyl)-4-methylbenzenesulfonamide (4f).** Colorless liquid. IR (film): 3277, 2931, 2251, 1599 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 0.85 (t, J = 7.24, 6.65 Hz, 3H), 1.00−1.30 (m, 7H), 1.40−1.75 (m, 3H), 2.40 (s, 3H), 2.50−2.70 (m, 2H), 3.30−3.50 (m, 1H), 4.60 (d, J = 7.87 Hz, 1H), 7.30 (d, J = 7.98 Hz, 2H), 7.80 (d, J = 8.31 Hz, 2H). EIMS (relative intensity): 309 (MH^+, 23), 268 (100), 223 (7), 155 (84), 91 (65). HRMS: for $C_{16}H_{24}N_2O_2S$ (M^+) calcd 308.1558, found 308.1543.

***N*-(2-Cyanoethyl)-4-methylbenzenesulfonamide (4g).**[16] White solid. Mp: 80−81 °C (lit.[16]mp >250 °C). IR (film): 3260, 2250, 1595 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 2.40 (s, 3H), 2.60 (t, J = 6.68, 6.59 Hz, 2H), 3.25 (q, J = 13.16, 6.59, 6.58 Hz, 2H), 5.15 (br, 1H), 7.35 (d, J = 8.04 Hz, 2H), 7.75 (d, J = 8.29 Hz, 2H). EIMS (relative intensity): 224 (M^+, 4), 184 (37), 155 (71), 91 (100). Anal. Calcd for $C_{10}H_{12}N_2O_2S$: C, 53.57; H, 5.36; N, 12.50. Found: C, 53.75; H, 5.31; N, 12.44.

***N*-(2-Cyano-1-methylcyclohexyl)-4-methylbenzenesulfonamide (4h).** White solid. Mp: 138−140 °C. IR (film): 3293, 2940, 2239, 1598 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 1.30 (s, 3H), 1.40−1.80 (m, 7H), 1.90−2.10 (m, 1H), 2.40 (s, 3H), 3.25−3.35 (dd, J = 4.09, 4.04 Hz, 1H), 4.90 (br, 1H), 7.30 (d, J = 8.15 Hz, 2H), 7.80 (d, J = 8.27 Hz, 2H). EIMS (relative intensity): 293 (MH^+, 4), 292 (M^+, 10), 224 (61), 210 (23), 155 (64), 91 (100). Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.62; H, 6.90; N, 9.59. Found: C, 61.57; H, 6.98; N, 9.56.

***N*-(2-Chlorocyclohexyl)-4-methylbenzenesulfonamide (6a).**[17] White solid. Mp: 100−102 °C. IR (film): 3255, 2947, 2869, 1922, 1596 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 1.20−1.40 (m, 3H), 1.55−1.75 (m, 3H), 2.10−2.30 (m, 2H), 2.40 (s, 3H), 3.10−3.20 (m, 1H), 3.60−3.70 (m, 1H), 4.85 (br, 1H), 7.30 (d, J = 8.04 Hz, 2H), 7.80 (d, J = 8.25 Hz, 2H). EIMS (relative intensity): 289 (M^+, ^{37}Cl, 8), 287 (M^+, ^{35}Cl, 22), 252 (18), 210 (100), 155 (89), 91 (65). Anal. Calcd for $C_{13}H_{18}ClNO_2S$: C, 54.26; H, 6.26; N, 4.87. Found: C, 54.55; H, 6.26; N, 4.71.

***N*-(2-Chlorocyclopentyl)-4-methylbenzenesulfonamide (6b).**[17] White solid. Mp: 86−87 °C. IR (film): 3266, 2976, 2879, 1908, 1598 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 1.30−1.50 (m, 1H), 1.60−2.00 (m, 3H), 2.10−2.25 (m, 2H), 2.40 (s, 3H), 3.50−3.60 (m, 1H), 4.05−4.15 (m, 1H), 4.80 (bd, J = 5.24 Hz, 1H), 7.35 (d, J = 8.28 Hz, 2H), 7.80 (d, J = 8.30 Hz, 2H). EIMS

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(relative intensity): 275 (M^+, ^{37}Cl, 5), 273 (M^+, ^{35}Cl, 13), 210 (69), 155 (63), 91 (100). Anal. Calcd for $C_{12}H_{16}ClNO_2S$: C, 52.65; H, 5.85; N, 5.12. Found: C, 52.54; H, 6.06; N, 5.00.

***N*-(2-Chloroethyl)-4-methylbenzenesulfonamide (6g).**[18] White solid. Mp: 97−98 °C. IR (film): 3278, 2961, 1598 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 2.40 (s, 3H), 3.30 (q, J = 12.00, 6.04, 5.93 Hz, 2H), 3.55 (t, J = 5.82, 5.76 Hz, 2H), 4.95 (br, 1H), 7.30 (d, J = 8.26 Hz, 2H), 7.75 (d, J = 8.28 Hz, 2H). EIMS (relative intensity): 235 (M^+, ^{37}Cl, 0.52), 233 (M^+, ^{35}Cl, 1.19), 184 (51), 155 (73), 91 (100). Anal. Calcd for $C_9H_{12}ClNO_2S$: C, 46.25; H, 5.14; N, 6.00. Found: C, 46.32; H, 5.19; N, 5.89.

***N*-(2-Azidocyclohexyl)benzoylamide (8a).**[7] White solid. Mp: 163−164 °C. IR (film): 3299, 3064, 2089, 1635, 1546 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 1.25−1.75 (m, 4H), 1.75−2.00 (m, 2H), 2.10−2.30 (m, 2H), 3.20−3.30 (m, 1H), 3.90−4.10 (m, 1H), 6.00−6.20 (br, 1H), 7.40−7.55 (m, 3H), 7.80 (d, J = 8.38 Hz, 2H). EIMS (relative intensity): 245 (MH^+, 6), 173 (13), 122 (10), 105 (100), 77 (38). Anal. Calcd for $C_{13}H_{16}N_4O$: C, 63.93; H, 6.56, N, 22.95. Found: C, 63.46; H, 6.46; N, 22.49.

***N*-(2-Cyanocyclohexyl)benzoylamide (9a).** White solid. Mp: 177−178 °C. IR (film): 3323, 3234, 3058, 2239, 1637, 1530 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 1.20−1.60 (m, 3H), 1.60−1.90 (m, 3H), 2.05−2.25 (m, 2H), 2.75−2.90 (m, 1H), 4.10−4.30 (m, 1H), 6.20−6.45 (m, 1H), 7.40−7.60 (m, 3H), 7.80 (d, J = 7.06 Hz, 2H). EIMS (relative intensity): 229 (MH^+, 6), 228 (M^+, 13), 160 (5), 122 (9), 105 (100), 77 (40). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.68; H, 7.02; N, 12.28. Found: C, 73.60; H, 7.09; N, 12.26.

***N*-(2-Aminoethyl)-4-methylbenzenesulfonamide (10).**[19] Azido derivative **2g** (55 mg, 0.23 mmol) was dissolved in methanol (5 mL), and 10% Pd−C (21 mg) was added. After being stirred for 20 h at room temperature under hydrogen atmosphere, the reaction mixture was filtered. After removal of the solvent, the product (46 mg, 94% yield) as white solid was obtained. Mp: 112−114 °C. IR (film): 3366, 3304, 2860, 1597 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 2.40 (s, 3H), 2.60−3.20 (m, 7H), 7.30 (d, J = 8.21 Hz, 2H), 7.80 (d, J = 8.26 Hz, 2H). EIMS (relative intensity): 215 (MH^+, 36), 198 (3), 185 (35), 155 (27), 91 (100). HRMS: for $C_9H_{15}N_2O_2S$ (MH^+) calcd 215.0869, found 215.0862.

***N*-(2-Methylactylcyclohexyl)-4-methylbenzenesulfonamide (11).** Nitrile **4a** (244 mg, 0.88 mmol) was dissolved in 3 mL of saturated methanolic HCl. After the mixture was stirred for 12 h at room temperature, the methanol was evaporated and the residue was diluted with 30 mL of ethyl acetate. The organic layer was washed with 10% aqueous $NaHCO_3$, water, and brine, respectively, and dried over Na_2SO_4. After removal of the solvent, the amino ester (252 mg, 92% yield) as a white solid was obtained by column chromatography (ethyl acetate as the eluent). Mp: 126−127 °C. IR (film): 3427, 3336, 1650 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 1.10−1.30 (m, 3H), 1.35−1.60 (m, 1H), 1.60−1.75 (m, 2H) 1.80−1.95 (m, 1H), 1.95−2.10 (m, 1H), 2.10−2.30 (m, 1H), 2.40 (s, 3H), 3.15−3.30 (m, 1H), 3.50 (s, 3H), 4.90−5.70 (br, 1H), 7.30 (d, J = 8.27 Hz, 2H), 7.75 (d, J = 8.27 Hz, 2H). EIMS (relative intensity): 311 (M^+, 16), 155 (100), 91 (88). HRMS: for $C_{15}H_{21}NO_4S$ (M^+) calcd 311.1191, found 311.1217.

***N*-(2-Aminocyclohexyl)benzoylamide (12).** Azido derivative **8a** (44 mg, 0.18 mmol) was dissolved in methanol (4 mL), and 10% Pd−C (18 mg) was added. After being stirred for 24 h at room temperature under hydrogen atmosphere, the reaction mixture was filtered. After removal of the solvent, the residue was purified by flash chromatography (methanol as the eluent) to give the product **12** (34 mg, 88% yield) as a white solid. Mp: 110−112 °C. IR (film): 3360, 3295, 1633 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ (ppm):1.10−1.80 (m, 8H), 1.90−2.25 (m, 2H), 2.40−2.60 (m, 1H), 3.70−3.80 (m, 1H), 6.20 (bd, J = 6.71 Hz, 1H), 7.30−7.50 (m, 3H), 7.70−7.85 (m, 2H). EIMS (relative intensity): 219 (MH^+, 1.23), 201 (0.99), 105 (58), 97 (100). HRMS: for $C_{13}H_{18}N_2O$ calcd 219.1498, found 219.1498.

***N*-(2-Methylactylcyclopentyl)-4-methylbenzenesulfonamide (13).** Nitrile **4b** (66 mg, 0.25 mmol) was dissolved in 2 mL of saturated methanolic HCl. After the mixture was stirred for 12 h at room temperature, the methanol was evaporated and the residue was diluted with 20 mL of ethyl acetate. The organic layer was washed with 10% aqueous $NaHCO_3$, water, and brine, respectively, and dried over Na_2SO_4. After removal of the solvent, the amino ester **13** (69 mg, 94% yield) as colorless liquid was obtained by column chromatography (ethyl acetate as the eluent). IR (film): 3399, 3269, 1671 cm^{-1}. ^1H NMR (CD_3COCD_3/TMS) δ (ppm): 1.30−1.50 (m, 1H), 1.50−1.80 (m, 4H), 1.80−2.00 (m, 1H), 2.40 (s, 3H), 2.55−2.70 (m, 1H), 3.15 (s, 3H), 3.50 (m, 2H), 7.30−7.40 (m, 2H), 7.70−7.80 (m, 2H). EIMS (relative intensity): 298 (MH^+, 11), 297 (M^+, 52), 265 (14), 141 (100). HRMS: for $C_{14}H_{20}NO_4S$ (MH^+) calcd 298.1145, found 298.1129.

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