Efficient Synthesis of Medium-Sized Cyclic Amines by Means of 2-Nitrobenzenesulfonamide

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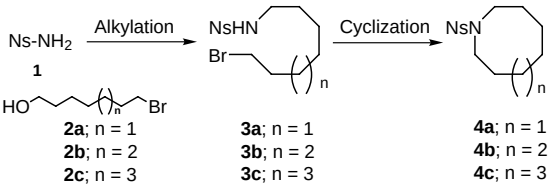
Abstract: Construction of medium-sized cyclic amines using 2-nitrobenzenesulfonamides is described. Under either conventional alkylation or Mitsunobu reaction conditions, the cyclization reaction proceeded efficiently to give eight- to ten-membered rings.

Key words: medium-sized cyclic amines, macrocyclization, 2-nitrobenzenesulfonamide, alkylation, Mitsunobu reaction

The construction of medium-sized cyclic amines is an important task in organic synthesis, since such structural units often constitute the frameworks of a variety of medicinally important natural products. Although there are numerous reports on the construction of medium-sized cyclic amines, only a few have implemented direct cyclization with nitrogen nucleophiles.[1,2] We have recently developed a novel methodology for transformation of primary amines to secondary amines using 2-nitrobenzenesulfonamides as an activating and a protecting group (Ns-strategy).[3–8] Furthermore, during the course of the total synthesis of lipogrammistin-A, a macrocyclic polyamine, we found that Ns-strategy is effective for the construction of the 18-membered ring (Scheme 1).[9] We envisioned that this strategy may prove to be a general protocol for the construction of medium-sized cyclic amines. Herein we report novel syntheses of eight- to ten-membered cyclic amines from ω-bromoalcohol by means of 2-nitrobenzenesulfonamide strategy.

As shown in Table 1, the ring closure reactions using 2-nitrobenzenesulfonamide were investigated with non-branched, simple substrates. Coupling between sulfonamide **1** and alcohol **2a**–**c** was performed under Mitsunobu conditions to give predominantly mono-alkylated products **3a**–**c**. Preliminary studies on the cyclization with **3a**–**c**, revealed that some what higher dilution conditions were necessary (0.01 M) to obtain reasonable yields. Thus, when acetonitrile solution of **3a**–**c** was slowly added (2 h) via a syringe pump to a mixture of tetrabutylammonium iodide and Cs_2CO_3 in acetonitrile at 60 °C, the cyclization proceeded smoothly to give the desired products **4a**–**c** in good yields.

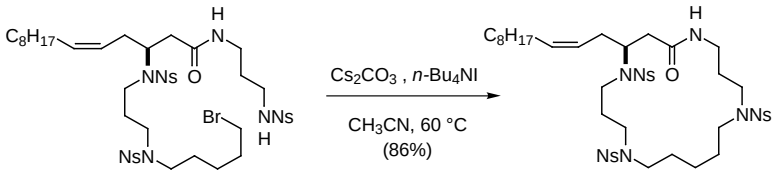
Table 1 Cyclization via Conventional Alkylation



Ring size	Alcohol	Alkylation[a] (yield %)	Cyclization[b] (yield %)
8	**2a**	**3a** (70)	**4a** (62)
9	**2b**	**3b** (67)	**4b** (64)
10	**2c**	**3c** (74)	**4c** (66)

[a] Alkylation conditions. PPh_3, DEAD, toluene–THF.[12]
[b] Cyclization conditions. Cs_2CO_3, CH_3CN, *n*-Bu_4NI, 60 °C.[12,13]

In order to perform the cyclization under Mitsunobu conditions, the precursors **6a**–**c** were prepared from *N*-Boc-nitrobenzensulfonamide **5**[10] (Table 2). Upon treatment of **5** with bromide **2a**–**c** with K_2CO_3 in DMF, the alkylation reaction proceeded smoothly to give *N*-Boc protected precursors. Subsequent acidic deprotection of the Boc group followed by basic methanolysis of trifluoroacetate with K_2CO_3 in methanol provided the cyclization precursors **6a**–**c**. Upon treatment of **6a**–**c** with DEAD and triphe-



Scheme 1

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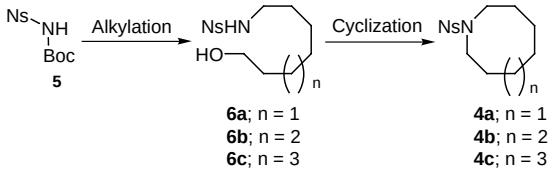
nylphosphine in 0.01 M solution of toluene-THF at room temperature, the desired cyclization reaction proceeded smoothly to afford **4a**–**c** in good yields.

Table 2 Cyclization via Mitsunobu Reaction



6a; n = 1
6b; n = 2
6c; n = 3

4a; n = 1
4b; n = 2
4c; n = 3

Ring size	Bromide	Alkylation[a] (yield %)	Cyclization[b] (yield %)
8	**2a**	**6a** (66)	**4a** (59)
9	**2b**	**6b** (85)	**4b** (57)
10	**2c**	**6c** (62)	**4c** (62)

[a] Alkylation conditions: 1) K_2CO_3, *n*-Bu_4NI, DMF, 60 °C. 2) TFA, CH_2Cl_2. 3) K_2CO_3, MeOH.[12]
[b] Cyclization conditions. PPh_3, DEAD, toluene–THF.[12]

In both protocols for the ring closures, the reactions proceeded successfully without using the branching effect.[11] Thus, Ns-strategy proved to be a powerful protocol for the construction of medium-sized rings, overriding the inherent entropic disadvantage of the ring closure. Considering the mildness of the alkylation and the deprotection conditions, Ns-strategy would be compatible with a variety of functional groups. Furthermore, the fact that both alcohols and halides served as starting materials would allow preparation of a wide range of nitrogen heterocycles. Further application of this methodology to the total syntheses of complex natural products is currently under investigation in our laboratories.

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(12) Experimental procedure for the introduction of Ns-amide and macrocyclization and spectral data for all new compounds are described below.
Representative Experimental Procedures. Synthesis of 3a: To a stirred solution of 2-nitrobenzenesulfonamide (3.20 g, 15.8 mmol), 7-bromo-1-heptanol (**2a**) (1.00 g, 5.13 mmol), and Ph_3P (1.80 g, 8.91 mmol) in toluene (9 mL) and THF (1.2 mL) was added DEAD (4 mL, 8.80 mmol, 40% in toluene) dropwise at 0 °C under argon atmosphere. The solution was stirred at 0 °C for 5 min, then at room temperature for 2.5 h. After removal of the solvent under reduced pressure, the remaining residue was purified by flash chromatography, (9:1 hexane–EtOAc) on a silica gel column, to give **3a** (1.36 g, 70%) as white powder. IR (film, cm^{-1}): 3346, 3096, 2933, 2857, 1539, 1440, 1414, 1360, 1341, 1166, 1125, 1060, 853, 782. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.29 (4 H, m), 1.33 (2 H, m), 1.52 (2 H, m), 1.81 (2 H, m), 3.10 (2 H, q, *J* = 6.8 Hz), 3.37 (2 H, t, *J* = 6.8 Hz), 5.23 (1 H, m), 7.76 (2 H, m), 7.87 (1 H, m), 8.14 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.2, 27.8, 28.1, 29.4, 32.5, 33.8, 43.7, 125.3, 131.0, 132.8, 133.5, 133.7, 148.0. FAB-MS: *m/z* 379 (MH^+); Anal. Calcd. for $C_{13}H_{20}BrN_2O_4S$: C, 41.17; H, 5.05; N, 7.39. Found: C, 41.24; H, 5.04; N, 7.30. Spectral data for **3b** (white powder): IR (film, cm^{-1}): 3346, 3099, 2930, 2856, 1592, 1539, 1440, 1414, 1360, 1342, 1165, 1125, 1061. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.26 (6 H, m), 1.39 (2 H, m), 1.53 (2 H, m), 1.83 (2 H, m), 3.10 (2 H, q, *J* = 6.8 Hz), 3.39 (2 H, t, *J* = 6.8 Hz), 5.23 (1 H, m), 7.75 (2 H, m), 7.87 (1 H, m), 8.15 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.4, 28.0, 28.6, 28.9, 29.6, 32.7, 34.0, 43.9, 125.4, 131.2, 132.8, 133.6, 133.8, 148.2. FAB-MS: *m/z* 393 (MH^+); HRMS (FAB): Found 393.0411 (MH^+), Calcd. 393.0413 ($C_{14}H_{22}BrN_2O_4S$, MH^+).
Spectral data for **3c** (white powder). IR (film, cm^{-1}): 3346, 3099, 2930, 2856, 1592, 1539, 1440, 1414, 1360, 1342, 1165, 1125, 1061. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25 (8 H, m), 1.40 (2 H, m), 1.54 (2 H, m), 1.83 (2 H, t, *J* = 4.0 Hz), 3.10 (2 H, q, *J* = 3.4 Hz), 3.40 (2 H, t, *J* = 3.4 Hz), 5.22 (1 H, m), 7.75 (2 H, m), 7.87 (1 H, m), 8.15 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.4, 28.0, 28.5, 28.8, 29.1, 29.5, 32.7, 34.0, 43.8, 125.3, 131.1, 132.7, 133.5, 133.8, 148.1. FAB-MS : *m/z* 407 (MH^+); Anal. Calcd. for $C_{15}H_{24}BrN_2O_4S$: C, 44.23; H, 5.69; N, 6.88. Found: C, 44.46; H, 5.71; N, 6.64.
Synthesis of 4a: To a stirred solution of Cs_2CO_3 (2.10 g, 6.45 mmol) and TBAI (980 mg, 2.65 mmol) in CH_3CN (3.00 mL) was added *N*-2-nitrobenzenesulfonyl-7-bromo-1-aminoheptane (**3a**) (500 mg, 1.32 mmol) in CH_3CN (24.0 mL) via syringe pump for 2 h at 60 °C, and stirred for additional 2 h at the same temperature. The reaction mixture was poured into water and extracted with EtOAc three times.

The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography (Et_2O) on a silica gel column to give **4a** (245 mg, 62%) as white powder. IR (film, cm^{-1}): 2929, 2857, 1542, 1456, 1373, 1344, 1164, 993. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.59 (6 H, m), 1.69 (4 H, m), 3.25 (4 H, t, *J* = 6.0 Hz), 7.52 (1 H, m), 7.61 (2 H, m), 7.84 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.8, 26.5, 27.7, 49.3, 123.9, 130.4, 131.4, 132.5, 133.3, 148.4. FAB-MS: *m/z* 299 (MH^+); HRMS (FAB): Found 299.0981(MH^+); Calcd 299.0995 ($C_{13}H_{19}N_2O_4S$, MH^+). Anal. Calcd for $C_{13}H_{19}N_2O_4S$: C, 52.33; H, 6.08; N, 9.39. Found: C, 52.29; H, 5.99; N, 9.35.

Spectral data for **4b** (white powder): IR (film, cm^{-1}): 2931, 2859, 1725, 1546, 1463, 1373, 1347, 1290, 1161, 1125, 851, 777, 742. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.32 (8 H, m), 1.57 (4 H, m), 3.25 (4 H, t, *J* = 8.0 Hz), 7.61 (1 H, m), 7.68 (2 H, m), 7.98 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.9, 27.9, 28.1, 47.8, 124.4, 129.0, 130.9, 131.8, 133.6, 148.4. FAB-MS: *m/z* 313 (MH^+); Anal. Calcd for $C_{14}H_{21}N_2O_4S$: C, 53.83; H, 6.45; N, 8.97. Found: C, 53.87; H, 6.29; N, 8.68.

Spectral data for **4c** (white powder): IR (film, cm^{-1}): 2928, 2855, 1542, 1463, 1373, 1346, 1160, 851. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.32 (10 H, m), 1.57 (4 H, m), 3.29 (4 H, t, *J* = 8.0 Hz), 7.59 (1 H, m), 7.67 (2 H, m), 7.97 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.2, 27.9, 28.3, 28.5, 48.7, 124.0, 130.6, 131.4, 133.2, 133.3, 148.3. FAB-MS: *m/z* 327 (MH^+); HRMS (FAB): Found 327.1311 (MH^+); Calcd. 327.1308 ($C_{15}H_{23}N_2O_4S$, MH^+); Anal. Calcd for $C_{15}H_{23}N_2O_4S$: C, 54.96; H, 6.74; N, 8.30. Found: C, 55.19; H, 6.79; N, 8.58.

Synthesis of 6a: To a stirred solution of *N*-Boc-2-nitrobenzenesulfonamide (**5**) (1.25 g, 4.14 mmol), K_2CO_3 (2.50 g, 18.1 mmol) and tetra-*n*-butylammonium iodide (40 mg, 0.11 mmol) in DMF (7 mL) was added 7-bromo-1-heptanol (770 mg, 3.98 mmol). The solution was stirred at 60 °C for 10 h and then poured into water. The mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was dissolved in CH_2Cl_2 (1 mL) and TFA (7 mL). After stirring for 1 h, the reaction mixture was concentrated. To the mixture in MeOH was added K_2CO_3 (1.00 g, 7.23 mmol), and stirred for 10 min. The reaction mixture was poured into water and extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. Recrystallization from ether–hexane afforded **6a** (1.00 g, 60%) as white powder. IR (film, cm^{-1}): 3343, 2933, 2859, 1543, 1413, 1364, 1339, 1165, 1126, 1059, 853, 783, 741. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.30 (4 H, m), 1.50 (2 H, m), 1.53 (4 H, m), 3.09 (2 H, m), 3.63 (2 H, m), 5.25 (1 H, m), 7.75 (2 H, m), 7.87 (1 H, m), 8.14 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 26.4, 28.8, 29.5, 32.5, 43.8, 62.9, 125.4, 131.1, 132.8, 133.5, 133.8, 149.8. FAB-MS: *m/z* 317 (MH^+); HRMS (FAB): Found 317.1180 (MH^+); Calcd 317.1177 ($C_{13}H_{21}O_2N_5S$, MH^+).

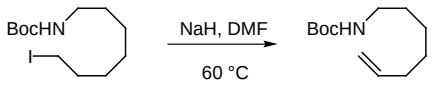
Spectral data for **6b** (white powder): IR (film, cm^{-1}): 3289, 2931, 2856, 1540, 1418, 1362, 1338, 1163, 1126, 1058. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.27 (8 H, m), 1.52 (4 H, m), 3.09 (2 H, m), 3.62 (2 H, m), 5.28 (1 H, m), 7.71 (2 H, m), 7.87 (1 H, m), 8.14 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 26.3, 28.9, 29.1, 29.5, 32.6, 43.8, 62.9, 125.3, 131.1, 132.7, 133.5, 133.8, 148.1. FAB-MS: *m/z* 331 (MH^+); HRMS (FAB): Found 331.1327 (MH^+); Calcd 331.1329 ($C_{14}H_{23}O_2N_5S$, MH^+).

Spectral data for **6c** (white powder): IR (film, cm^{-1}): 3287, 2926, 2853, 1541, 1360, 1333, 1163, 1126, 1062, 854, 780, 728. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25 (10 H, m), 1.53 (4 H, m), 3.09 (2 H, q, *J* = 6.8 Hz), 3.63 (2 H, t, *J* = 6.8 Hz), 5.27 (1 H, m), 7.74 (2 H, m), 7.87 (1 H, m), 8.14 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.6, 26.4, 28.9, 29.2, 29.3, 29.5, 32.7, 43.8, 63.0, 125.3, 131.1, 132.7, 133.5, 133.8, 148.0. FAB-MS: *m/z* 345 (MH^+); HR MS (FAB): Found 345.1407 (MH^+); Calcd 345.1414 ($C_{15}H_{25}O_2N_5S$, MH^+).

Representative Experimental Procedure. Synthesis of 4a under Mitsunobu Conditions

To a stirred solution of Ph_3P (463 mg, 2.29 mmol) and *N*-(2-nitrobenzenesulfonyl)-7-hydroxy-1-aminoheptane(**6a**) (200 mg, 0.63 mmol) in toluene (48 mL)and THF (16 mL) was added DEAD (1.05 mL, 2.31 mmol, 40% in toluene) drop wise and stirred for 3 h. The reaction mixture was concentrated in vacuo, the residue was purified by flash chromatography (1:4, EtOAc–hexane) on a silica gel column to give **4a** (112 mg, 59%) as white powder.

(13) Attempted macrocyclization of *N-tert*-Butoxycarbonyl-7-iodo-1-aminoheptane (**7**) was failed to the desired reaction as shown in Scheme 2. Treatment of **7** with sodium hydride in DMF at room temperature, the starting material was completely recovered. Upon heating to 60 °C, the dehydroiodination reaction was proceeded to give **8**.



7 **8** (40%)

Scheme 2