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Traceless solid-phase synthesis of multiple sulfonamide-containing cyclic sulfides exploiting microwave irradiation

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ABSTRACT

In this Letter, a new synthetic method of sulfonamide-containing cyclic sulfides using a microwave-assisted traceless solid-phase approach is described. Using this new method, many highly pure cyclic sulfides were efficiently synthesized based on intramolecular alkylation of the sulfides followed by elimination of the desired products from the generated sulfonium salts.

Compounds having sulfonamide-containing cyclic sulfide skeletons (**A**–**C**, Fig. 1) are known to show a number of intriguing biological activities, such as antimalarial effect,[1] VLA-4 antagonistic effect,[2] RyR receptors modulatory effect,[3] antiobesity effect,[4] and inhibitory effect on matrix metalloproteinase,[5] TACE,[6] phenylethanolamine *N*-methyltransferase,[7] FKBP12,[8] carbonic anhydrase,[9] IKK2,[10] and type II 17β-hydroxysteroid dehydrogenase.[11] Therefore, it is believed that these skeletons and their analogs are very attractive templates for chemical libraries to generate novel bioactive compounds in high-throughput screenings (HTS).

To generate a high rate of hits in HTS, diversity of compounds is extremely important. However, most reported chemical libraries are designed based on a single scaffold,[12] the diversity of which is relatively low because all compounds in the library have the same structure as the scaffold. One of the purposes of our work is to construct highly diverse chemical libraries containing multiple scaffolds using the same synthetic approach. With respect to cyclic sulfide skeletons, our method can efficiently provide not only existing scaffolds[1–11] (**A**–**C**, Fig. 1) but also novel scaffolds (**D**–**G**, Fig. 1) we first report herein, on the selection of appropriate building blocks.

Another purpose of our work is to synthesize drug-like compounds without the tedious purification steps. Compounds **A**–**C** have previously been synthesized using conventional solution-phase methods[1–11], although these methods are somewhat problematic for development of chemical libraries. Solution-phase methods are inappropriate for multi-step syntheses involved in chemical library development due to the purification required in each step. Although solid-phase methods can omit purification of synthetic intermediates, they generate final products with resin-tethering substituents that are polar. This often compromises the bioavailability and reduces the structural diversity of the chemical library. In addition, products obtained by cleavage of the resin in the final step are often mixtures of the desired compounds with many kinds of impurities generated by incomplete reactions on the polymer support in the previous steps. We have developed new traceless solid-phase synthesis where the intramolecular alkylation of the amine or sulfide and the following debenzylation of the resulting ammonium or sulfonium salts by S_N2 reaction afford the desired cyclic products. While the last debenzylation step might accompany S_N2 reaction at the intracyclic α-carbon atoms of

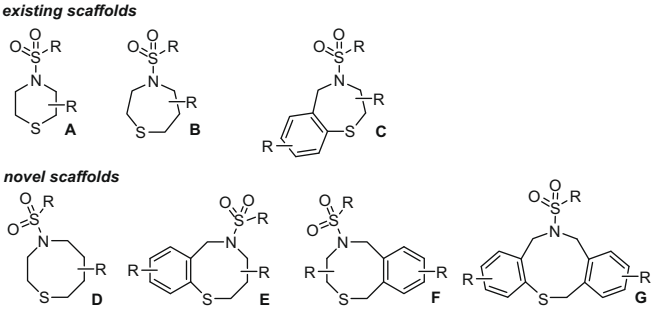

Figure 1. Sulfonamide-containing cyclic sulfides.

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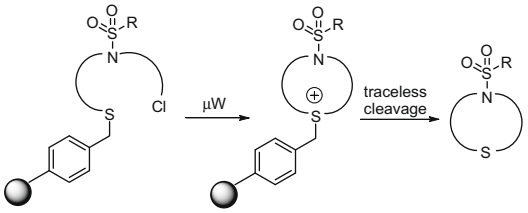


Scheme 1.

the sulfonium cation, the resulting alkyl iodides recyclize to regenerate the sulfonium salt or remain intact on the solid supports, not reducing the purity of the products. In addition, most of the presumably unreacted intermediates are not detached from solid supports at the end of the reaction. We have previously reported the synthesis of thiomorpholin-3-ones as cyclic sulfides and two kinds of cyclic tertiary amines using this strategy.[13] In those syntheses, intermediates possessing α-chloroacetamide moiety with strong alkylating activity were cyclized under mild conventional heating conditions. In the present study, we have established the synthetic method of sulfonamide-containing cyclic sulfides using a similar strategy (Scheme 1). Since the alkyl chloride moiety in cyclization precursors showed much weaker reactivity, microwave irradiation was used to promote the ring-forming reaction under higher temperature. Interestingly, conventional heating was not as effective as microwave irradiation as described below. A polymer-supported base was used as hydrogen chloride scavenger.

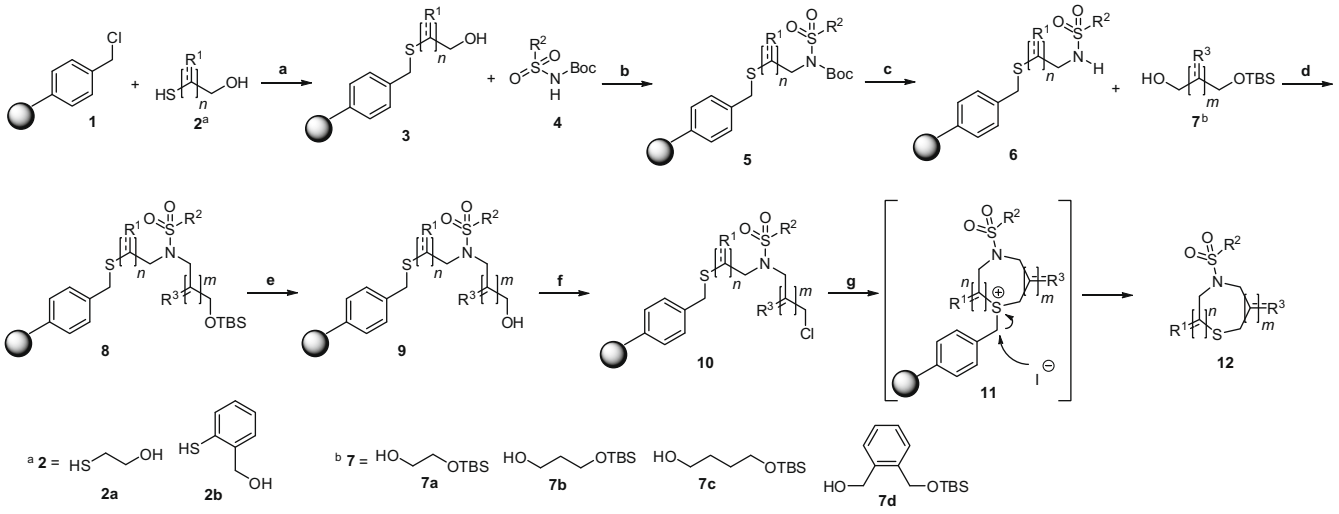
The synthesis began with nucleophilic displacement of the benzyl chloride on the Merrifield resin **1** with the sulfanylalcohols **2** (Scheme 2). Next, under the traditional Mitsunobu conditions with the *N*-Boc-protected sulfonamides **4**, the polymer-supported alcohols **3** were converted to the *N*-alkyl-*N*-Boc-proctected sulfonamides **5**, which in turn provided the deprotected sulfonamides **6** by *n*-$BuNH_2$.[14] **6** were then alkylated by the mono-TBS-protected diols **7** under the improved Mitsunobu conditions with *N,N,N′,N′*-tetramethylazodicarboxamide (TMAD) and *n*-Bu_3P.[15] The resulting **9** was transformed into the alkyl halides **10**. Intramolecular cyclization of **10** and debenzylation of the sulfonium salts **11** were carried out under microwave irradiation to provide the product **12** in high purity without purification by column chromatography.[16,17] The cyclization reaction was also carried out under conventional heating conditions in a sealed tube at the same temperature (180 °C) for the same reaction time (1 h) in order to assess the utility of microwave irradiation. Interestingly, microwave heating gave the much better yield of **12a** (88%, Table 1, entry 1) than conventional heating (27%). It implied that the non-thermal effect of microwave promoted cyclization and/or cleavage.[18]

To demonstrate the usefulness of this approach, several sulfonamide-containing cyclic sulfides were synthesized. The representative results are shown in Table 1. Various aryl and alkyl groups were introduced into R^2 giving compounds with high purity and good total yield (entries 1–5). A compound with a functional group such as a basic nitrogen could also be obtained (entry 4). Construction of seven- and eight-membered rings (entries 6 and 7) and condensed rings (entries 8–11), both of which are regarded as novel scaffolds, was also possible by switching the building blocks. This finding indicates that this synthetic route can expand diversity of the libraries without any difficulties, making the discovery of new bioactive compounds in HTS more favorable. It is generally known that solution-phase construction of medium-sized rings containing eight- and nine-membered rings is often attended with undesirable intermolecular reactions and therefore results in low yields or failure. By contrast, our method afforded the eight- and nine-membered rings in yields comparable to those of the six- and seven-membered rings (entries 1 and 6 vs entries 7, 8, and 11). The pseudo high-dilution effect on the solid support probably favored the intramolecular cyclization over the intermolecular side reaction.[19]

In conclusion, a novel traceless solid-phase synthesis of multiple sulfonamide-containing cyclic sulfides based on the Merrifield resin has been developed. Using this new method, we are currently constructing novel and diverse chemical libraries for HTS. Information of the biological activity of the synthesized multiple sulfonamide-containing cyclic sulfides will be reported in due course.

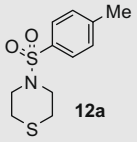
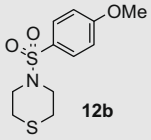
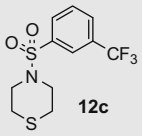
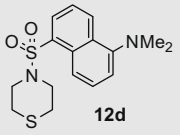
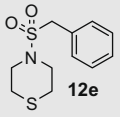
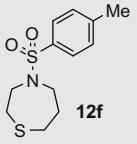
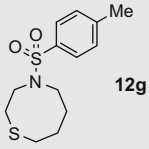
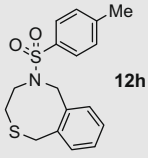
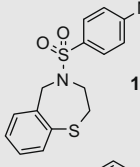
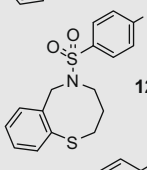
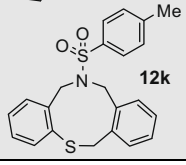
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.028.



Scheme 2. Reagents and conditions: (a) **2** (3 equiv), DBU (4 equiv), DMF, rt, 24 h; (b) **4** (4 equiv), PPh_3 (4 equiv), DEAD (4 equiv), THF, rt, 24 h; (c) *n*-$BuNH_2$, rt, 24 h; (d) **7** (4 equiv), TMAD (4 equiv), *n*-Bu_3P (4 equiv), THF, rt, 24 h; (e) 1 M TBAF/THF, rt, 24 h; (f) Cl_3CCCl_3 (4 equiv), PPh_3 (4 equiv), CH_2Cl_2, rt, 24 h; (g) CsI (2 equiv), piperidinomethyl polystyrene (2 equiv), dioxane, water, 180 °C, 1–2 h.

Table 1
Syntheses of sulfonamide-containing cyclic sulfides **12**

Entry	2	7	Time of condition g (h)	Product	Yield[a] (%) purity[b] (%)
1	**2a**	**7a**	1	 **12a**	88 (98)
2	**2a**	**7a**	1	 **12b**	91 (98)
3	**2a**	**7a**	1	 **12c**	89 (96)
4	**2a**	**7a**	1	 **12d**	62 (94)
5	**2a**	**7a**	1	 **12e**	70 (98)
6	**2a**	**7b**	1	 **12f**	68 (97)
7	**2a**	**7c**	1	 **12g**	71 (91)
8	**2a**	**7d**	1	 **12h**	93 (98)
9	**2b**	**7a**	2	 **12i**	62 (98)
10	**2b**	**7b**	2	 **12j**	53 (98)
11	**2b**	**7d**	2	 **12k**	74 (99)

[a] Isolated overall yields (seven steps) based on the Merrifield resin **1**.
[b] Reverse-phase HPLC was carried out using CH_3CN/20 mM phosphate buffer (pH 6.5). Flow rate: 1 ml/min. Column: ODS. HPLC purities were determined by summation of integrated HPLC peak areas at 210 nm.

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13. Some other examples of solid-phase synthesis accompanied by cyclization on the solid support revealed that the target heterocycles showed high purity without further post-cleavage purification, see: (a) Saruta, K.; Ogiku, T. *Chem. Lett.* **2007**, *36*, 1430–1431; (b) Saruta, K.; Ogiku, T. *Tetrahedron Lett.* **2008**, *49*, 424–427; (c) Saruta, K.; Ogiku, T. *Chem. Lett.* **2008**, *37*, 820–821.
14. *N*-Boc groups are generally cleaved by TFA or other strong acids, which are relatively troublesome to handle, and these may cause decrease in yield and purity and restrict the number of available building blocks, thereby lowering diversity of the chemical library. To avoid these disadvantages, *n*-$BuNH_2$ was adopted as a mild reagent for deprotection. For other examples of cleavage by amines, see: Leif, G.; Kerstin, G.; Ulf, R. *Acta Chem. Scand. B* **1987**, *41*, 18–23.
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16. The typical experimental procedure is as follows: To Merrifield resin **1** (20.0 g, 38.8 mmol, Polymer Laboratories; 1.94 mmol/g) in DMF (200 ml) were added DBU (23.2 ml, 155 mmol) and sulfanylethanol **2** (9.09 ml, 116 mmol) at 0 °C. After stirring for 10 min, the whole was allowed to stir at room temperature for 24 h. The resin was washed with DMF (×5), water (×5), MeOH (×5), THF (×5), Et_2O (×5), and MeOH (×5) and dried in vacuo (**3**: 21.4 g; equivalent to 1.81 mmol/g). To a mixture of the resin **3** (11.9 g, 21.6 mmol), *N*-(*tert*-Butoxycarbonyl)-*p*-toluenesufonamide **4** (23.4 g, 86.4 mmol), and PPh_3 (22.7 g, 86.4 mmol) in THF (200 ml) was added dropwise 40% toluene solution of DEAD (40 ml, 86.4 mmol) at 0 °C for 30 min. After stirring for 10 min, the whole was allowed to stir at room temperature for 24 h. The resin was washed with CH_2Cl_2 (×5), THF (×5), MeOH (×5), THF (×5), Et_2O (×5), and MeOH (×5) and dried in vacuo (**5**: 21.4 g; equivalent to 1.17 mmol/g). To the resin **5** (3.08 g, 3.6 mmol) was added *n*-$BuNH_2$ (20 ml), and the whole was allowed to stir at room temperature for 24 h. The resin was washed with Et_3N-DMF (1:4, x5), DMF (×5), CH_2Cl_2 (×5), THF (×5), Et_2O (×5), and MeOH (×5) to give **6**. To a mixture of the obtained resin **6**, 2-(*tert*-Buthyldimethylsilanyloxy)ethanol **7** (2.54 g, 14.4 mmol) and *n*-Bu_3P (3.6 g, 14.4 mmol) in THF (200 ml) was added *N,N,N′,N′*-tetramethylazodicarboxamide (2.48 g, 14.4 mmol) at 0 °C. After stirring for 10 min, the whole was allowed to stir at room temperature for 24 h. The resin was washed with water (×3), DMF (×5), MeOH (×5), THF (×5), Et_2O (×5), and MeOH (×5) to give **8**. To the resin **8** was added 1 M THF solution of TBAF (25 ml), and the whole was allowed to stir at room temperature for 24 h. The resin was washed with THF (×5), MeOH (×5), THF (×5), and MeOH (×5) to give **9**. The obtained resin **9** was swollen with a mixture of PPh_3 (3.78 g, 14.4 mmol), hexachloroethane (3.41 g, 14.4 mmol), and CH_2Cl_2 (40 ml) and the mixture was stirred for 24 h at room temperature. The resin was then washed with CH_2Cl_2 (×5), MeOH (×5), THF (×5), Et_2O (×5), and MeOH (×5) to give **10**. To the resin **10** were added CsI (312 mg, 1.2 mmol), piperidinomethyl polystyrene (400 mg, 1,2 mmol, Polymer Laboratories; 3.0 mmol/g), dioxane (12 ml), and water (3 ml). The mixture was then heated in a microwave at 180 °C for 1 h. The resin was washed with water (×3), MeOH-$CHCl_3$ (1:4, x3), and MeOH (×5) and the filtrate was evaporated. The residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$. The organic layer was washed with 10% aqueous $Na_2S_2O_3$ and brine and dried with Na_2SO_4. The solvent was evaporated to provide product **12a** as pale yellow solid (130 mg, 88%).
    All products gave satisfactory 400 MHz ^1H NMR, 100 MHz ^{13}C NMR, IR and MS spectra. The spectral data of **12** are given below.
    Compound **12a**: 4-[(4-Methylphenyl)sulfonyl]-1,4-thiazaperhydroine: ^1H NMR (400 MHz, DMSO-d_6): δ 2.42 (3H, s), 2.64–2.67 (4H, m), 3.16–3.18 (4H, m), 7.46 (2H, d, J = 8.19 Hz), 7.63 (2H, d, J = 8.19 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 27.3, 47.9, 127.5, 129.8, 133.8, 143.8; IR (ATR) ν_{max}: 1336, 1160, 894, 715, 703, 584, 545; HRMS (ESI): calculated for $C_{11}H_{16}NO_2S_2$ $[M+H]^+$ 258.0616, found 258.0626.
    Compound **12b**: 4-[(4-Methoxyphenyl)sulfonyl]-1,4-thiazaperhydroine : ^1H NMR (400 MHz, DMSO-d_6): δ 2.65–2.67 (4H, m), 3.14–3.17 (4H, m), 3.86 (3H, s), 7.16 (2H, d, J = 8.70 Hz), 7.67 (2H, d, J = 8.70 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3, 47.9, 55.6, 114.4, 128.3, 129.5, 163.1; IR (ATR) ν_{max}: 1258, 1156, 1093, 899, 853, 705, 583, 555; HRMS (ESI): calculated for $C_{11}H_{16}NO_3S_2$ $[M+H]^+$ 274.0566, found 274.0578.
    Compound **12c**: 4-{[(3-(Trifluoromethyl)phenyl]sulfonyl}-1,4-thiazaperhydroine: ^1H NMR (400 MHz, DMSO-d_6): δ 2.67–2.69 (4H, m), 3.26–3.29 (4H, m), 7.93 (1H, t, J = 7.94 Hz), 7.99 (1H, s), 8.09 (1H, d, J = 7.94 Hz), 8.14 (1H, d, J = 7.94 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3, 47.9, 123 (q, J = 271 Hz), 124.3 (q, J = 3.80 Hz), 129.6 (q, J = 3.60 Hz), 130.1, 130.5, 132.0 (q, J = 33.5 Hz), 138.4; IR (ATR) ν_{max}: 1165, 1124, 1068, 693, 568; HRMS (ESI): calculated for $C_{11}H_{13}NO_2F_3S_2$ $[M+H]^+$ 312.0345, found 312.0334.
    Compound **12d**: 4-{[(5-(Dimethylamino)naphthyl]sulfonyl}-1,4-thiazaperhydroine: ^1H NMR (400 MHz, DMSO-d_6): δ 2.59–2.62 (4H, m), 2.84 (6H, s), 3.43–3.45 (4H, m), 7.28 (1H, d, J = 7.68 Hz), 7.60–7.68 (2H, m), 7.12–7.13 (1H, m), 8.20 (1H, d, J = 8.70 Hz), 8.52 (1H, d, J = 8.45 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3, 45.4, 47.3, 115.3, 119.4, 123.1, 128.1, 130.1, 130.3, 130.7, 133.5, 151.8; IR (ATR) ν_{max}: 1318, 1080, 913, 568; HRMS (ESI): calculated for $C_{16}H_{21}N_2O_2S_2$ $[M+H]^+$ 337.1038, found 337.1030.
    Compound **12e**: 4-(Benzylsulfonyl)-1,4-thiazaperhydroine: ^1H NMR (400 MHz, DMSO-d_6): δ 2.55–2.57 (4H, m), 3.31–3.32 (4H, m), 4.43 (2H, s), 7.35–7.42 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 48.0, 57.6, 128.7, 128.9, 130.4, 130.7; IR (ATR) ν_{max}: 1149, 899, 699, 528; HRMS (ESI): calculated for $C_{11}H_{16}NO_2S_2$ $[M+H]^+$ 258.0616, found 258.0623.
    Compound **12f**: 4-[(4-Methylphenyl)sulfonyl]-1,4-thiazaperhydroepine: ^1H NMR (400 MHz, DMSO-d_6): δ 1.86–1.92 (2H, m), 2.39 (3H, s), 2.67–2.74 (4H, m), 3.32–3.41 (4H, m), 7.41 (2H, d, J = 8.19 Hz), 7.69 (2H, d, J = 8.19 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 31.0, 31.9, 35.5, 48.8, 53.8, 126.8, 129.7, 136.8, 143.2; IR (ATR) ν_{max}: 1329, 1156, 714, 546; HRMS (ESI): calculated for $C_{12}H_{18}NO_2S_2$ $[M+H]^+$ 272.0773, found 272.0787.
    Compound **12g**: 4-[(4-Methylphenyl)sulfonyl]-1,4-thiazaperhydroocine: ^1H NMR (400 MHz, DMSO-d_6): δ 1.71–1.77 (2H, m), 1.85–1.91 (2H, m), 2.39 (3H, s), 2.71–2.73 (2H, m), 2.90–2.93 (2H, m), 3.09–3.11 (2H, m), 3.29–3.32 (2H, m), 7.42 (2H, d, J = 7.94 Hz), 7.66 (2H, d, J = 7.94 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 23.6, 27.0, 31.6, 33.5, 49.6, 51.0, 127.2, 129.7, 134.9, 143.3; IR (ATR) ν_{max}: 1324, 1155, 693, 647, 591, 546; HRMS (ESI): calculated for $C_{13}H_{20}NO_2S_2$ $[M+H]^+$ 286.0929, found 286.0947.
    Compound **12h**: 5-[(4-Methylphenyl)sulfonyl]-1*H*,3*H*,4*H*,6*H*-benzo[*f*]1,4-thiazaperhydroocine: ^1H NMR (400 MHz, DMSO-d_6): δ 2.42 (3H, s), 2.46–2.52 (2H, m), 3.49–3.52 (2H, m), 4.03 (2H, s), 4.42 (2H, s), 7.21–7.31 (4H, m), 7.44 (2H, d, J = 8.19 Hz), 7.73 (2H, d, J = 8.19 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 29.3, 32.9, 50.4, 51.0, 127.1, 127.7, 129.1, 129.9, 130.5, 134.3, 136.0, 136.9, 143.6; IR (ATR) ν_{max}: 1330, 1156, 718, 651, 543; HRMS (ESI): calculated for $C_{17}H_{20}NO_2S_2$ $[M+H]^+$ 334.0929, found 334.0922.
    Compound **12i**: 4-[(4-Methylphenyl)sulfonyl]-2*H*,3*H*,5*H*-benzo[*f*]1,4-thiazaperhydroepine: ^1H NMR (400 MHz, DMSO-d_6): δ 2.37 (3H, s), 2.77–2.79 (2H, m), 3.65–3.52 (2H, m), 4.51 (2H, s), 7.27–7.32 (2H, m), 7.35 (2H, d, J = 7.94 Hz), 7.41–7.47 (2H, m), 7.60 (2H, d, J = 7.94 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 33.8, 52.3, 54.0, 127.0, 128.1, 128.2, 129.7, 130.4, 132.9, 136.0, 137.0, 142.1, 143.3; IR (ATR) ν_{max}: 1327, 1149, 1090, 1071, 1054, 553, 543; HRMS (ESI): calculated for $C_{16}H_{18}NO_2S_2$ $[M+H]^+$ 320.0773, found 320.0786.
    Compound **12j**: 5-[(4-Methylphenyl)sulfonyl]-2*H*,3*H*,4*H*,6*H*-benzo[*g*]1,5-thiazaperhydroocine: ^1H NMR (400 MHz, DMSO-d_6): δ 1.66–1.72 (2H, m), 2.41 (3H, s), 2.72–2.75 (2H, m), 3.30–3.36 (2H, m), 4.58 (2H, s), 7.32–7.45 (5H, m), 7.59 (1H, d, J = 7.68 Hz), 7.76 (2H, d, J = 8.45 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 29.3, 36.5, 47.1, 51.9, 127.1, 129.1, 129.8, 131.5, 135.0, 136.6, 137.2, 141.7, 143.2; IR (ATR) ν_{max}: 1154, 1092, 749, 715, 653, 606; HRMS (ESI): calculated for $C_{17}H_{20}NO_2S_2$ $[M+H]^+$ 334.0929, found 334.0917.
    Compound **12k**: 12-[(4-Methylphenyl)sulfonyl]-6*H*,11*H*,13*H*-dibenzo[*b*,*g*]1,5-thiazaperhydroonine: ^1H NMR (400 MHz, DMSO-d_6): δ 2.45 (3H, s), 4.14 (2H, s), 4.21 (2H, s), 4.47 (2H, s), 7.00–7.14 (5H, m), 7.21–7.29 (2H, m), 7.36–7.38 (1H, m), 7.48 (2H, d, J = 8.45 Hz), 7.84 (2H, d, J = 8.45 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 37.9, 47.4, 49.7, 127.3, 127.7, 128.3, 128.4, 128.6, 129.8, 130.3, 131.3, 131.4, 133.9, 134.8, 136.8, 137.4, 137.7, 141.1, 143.4; IR (ATR) ν_{max}: 1327, 1150, 909, 719, 614, 527; HRMS (ESI): calculated for $C_{22}H_{22}NO_2S_2$ $[M+H]^+$ 396.1086, found 396.1074.
17. Initially, the last cyclization–debenzylation step was run by refluxing the mixed solvent of dioxane and water for 24 h in the presence of only CsI under conventional heating condition. However, the product (**12a**) was formed in only 25% yield, suggesting that more vigorous conditions were required to facilitate this reaction. We then tried running the reaction in the microwave at 180 °C for 1 h and the yield increased to over 90%. Unfortunately, impurities probably generated under the acidic condition by hydrolysis of resin-bound benzyl halides were detected by ^1H NMR. To scavenge the acids and improve purity, piperidinomethyl polystyrene was added. Addition of Triethylamine also gave a similar result regarding yield and purity.
18. For other examples about the non-thermal effect of microwave, see: (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223; (b) de la Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164–178.
19. Lee, J.; Griffin, J. H. *J. Org. Chem.* **1996**, *61*, 3983.