Highly Efficient and Diastereoselective Construction of Tricyclic Pyrrolidine-Fused Benzo[*b*]thiophene 1,1-dioxide Derivatives *via* 1,3-Dipolar [3 + 2] Cycloaddition

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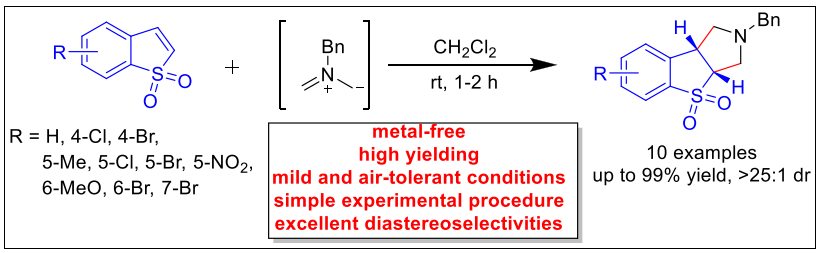

A rapid and highly efficient 1,3-dipolar [3 + 2] cycloaddition of nonstabilized azomethine ylides generated *in situ* with benzo[*b*]thiophene 1,1-dioxides as the dipolarophiles has been developed. The efficient method affords tricyclic pyrrolidine-fused benzo[*b*]thiophene 1,1-dioxide derivatives in high to excellent yields (up to 99%) with excellent diastereoselectivities (up to >25:1 dr) under mild reaction conditions. The structure of a typical product was confirmed by X-ray crystallography.

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INTRODUCTION

The fused polycyclic pyrrolidine skeletons are privileged structural motifs that are frequently encountered in biologically active natural products, with significant applications in the pharmaceutical and biological community [1]. Among them, the tricyclic pyrrolidine motif [2] is the key structural moiety in alkaloids and biologically active compounds, such as Rivastigmine analogs [3] which exhibit the significant inhibitory effects on acetylcholinesterase, as well as, the tricyclic pyrrolidine display biological activity, for example, dipeptidyl peptidase IV (DPP-4) inhibitors, was identified [4]. As a result, the development of efficient methods for the construction of such frameworks have triggered increasing interest in organic and medicinal chemistry [5]. In general, the 1,3-dipolar cycloaddition represents a powerful methodology for the expedient regiospecific and stereospecific synthesis of five-membered ring N, O, or S-containing heterocycles [6]. In particular, the 1,3-dipolar [3 + 2] cycloaddition of azomethine ylides with activated olefins has become one of the most useful and well-established methods for the preparation of various substituted pyrrolidines. Azomethine ylides of nonstabilized type generated *in situ* are highly reactive intermediates [7], with activated alkenes [7a–f], aromatic ketones [7g], aromatic aldehydes [7h, i], isatoic anhydrides [7j], phthalic anhydrides [7k], or stable dipoles [7l] to build five or six-membered heterocycles in a single step.

On the other hand, benzo[*b*]thiophene 1,1-dioxides [8] are highly electrophilic reagents, which perform as dipolarophiles and participate in 1,3-dipolar cycloaddi tions with azomethine ylides to access tricyclic pyrrolidine [9]. Moreover, in 2017, the Deng group first reported highly efficient copper-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with benzo[*b*] thiophene 1,1-dioxides, providing elegant access to chiral tricyclic pyrrolidine-fused benzo[*b*]thiophene 1,1-dioxide derivatives [9a]. Very recently, the Fukuzawa group uncovered the asymmetric [3 + 2] dipolar cycloaddition reaction with benzo[*b*]thiophene 1,1-dioxides and azomethine ylides catalyzed by metal complex controlled to give exo-cycloadducts or endo-cycloadducts in good yield with high stereoselectivity [9b]. However, the reaction needed to use metal catalysts. In 2006, the Westwood group used benzo[*b*]thiophene sulfone in the thermal cycloaddition reaction with azomethine ylides sources. However, the reaction resulted in low yields and diastereoselectivities and required 3 days at high temperatures [9c]. Here, we would like to describe a new clean and rapid route for pyrrolidine-fused benzo[*b*] thiophene 1,1-dioxide derivatives without transition metal catalysts *via* [3 + 2] cycloaddition of azomethine

ylides generated from *N*-(methoxymethyl)-*N*-(trimethyl silylmethyl)benzylamine with benzo[*b*]thiophene 1,1-dioxides under mild and air-tolerant reaction conditions.

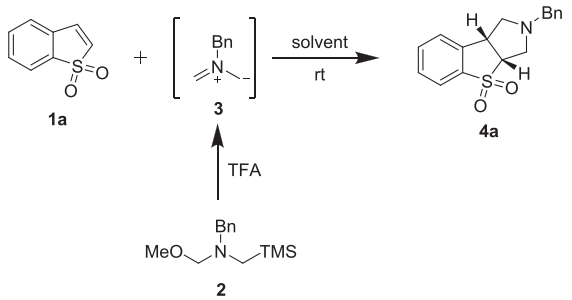
RESULTS AND DISCUSSION

In our initial attempt, benzo[*b*]thiophene sulfones **1a** was allowed to react with nonstabilized azomethine ylide **3**, formed from *N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzyl-amine **2** in the presence of trifluoroacetic acid (TFA). The results of these experiments are summarized in Table 1. To our delight, the transformation proceeded smoothly in 1,2-dichloroethane (DCE) at room temperature for 6 h and to give pyrrolidine-fused benzo[*b*]thiophene 1,1-dioxide **4a** in 90% yield with exclusive diastereoselectivity (>25:1 dr). In addition, the relative configuration of product **4a** was determined by X-ray crystal structure [10]. In order to optimize reaction conditions, different reaction solvents were screened, and CH_2Cl_2 was found to give optimal yields. The reaction can be carried out in $CHCl_3$ and CH_3CN with comparable yields and diastereoselectivities (>25:1 dr) (Table 1, entries 2 and 6) as that in DCE (Table 1, entries 3 and 4), whereas other solvents, such as tetrahydrofuran, 1,4-dioxane, toluene, and Et_2O, could readily afford the normal annulation product in inferior yields upon prolonging the reaction time (Table 1, entries 5 and 7–10). Importantly, the annulation proceeded smoothly with 50 mol % or even 10 mol % of TFA with retained diastereoselectivity (>25:1 dr), although a longer time was required with 63% and 45% yield, respectively (entries 11 and 12). Therefore, the best reaction conditions have been determined in CH_2Cl_2 at room temperature for a duration of 1 h.

With the optimized conditions in hand, we subsequently investigated the substrate scope and limitation of the formation of pyrrolidine-fused benzo[*b*]thiophene 1,1-dioxide derivatives. A variety of benzo[*b*]thiophene sulfones **1** bearing electron-neutral, electron-rich, and electron-poor substituents on the phenyl group were employed in the reaction under the optimized conditions, and the scope of substrates is summarized in Table 2. The benzo[*b*]thiophene sulfones **1** reacted smoothly with

Table 1

Optimization of the reaction conditions.[a]

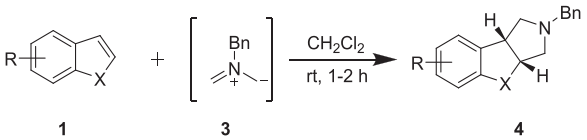


Entry	Solvent	Time (h)	Yield (%)[b]	dr[c]
1	DCE	6	90	>25:1
2	$CHCl_3$	3	92	>25:1
3	CH_2Cl_2	1	95	>25:1
4	CH_2Cl_2	2	95	>25:1
5	THF	6	83	>25:1
6	MeCN	12	91	>25:1
7	Toluene	12	72	>25:1
8	1,4-Dioxane	24	52	>25:1
9	Et_2O	12	61	>25:1
10	EtOAc	12	76	>25:1
11[d]	CH_2Cl_2	48	45	>25:1
12[e]	CH_2Cl_2	24	63	>25:1

[a]Unless noted otherwise, reactions were performed with **1a** (0.1 mmol), **2** (0.12 mmol), and TFA (0.12 mmol) in solvent (1.0 mL) at room temperature.
[b]Isolated yield.
[c]Determined by ^{1}H-NMR analysis.
[d]**2a** with TFA (0.012 mmol) present in 10% catalytic amounts.
[e]**2a** with TFA (0.06 mmol) present in 50% catalytic amounts.

Table 2

Substrate scope and limitation of the 1,3-dipolar cycloaddition.[a]

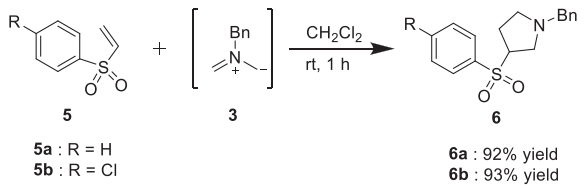


Entry	R	Time (h)	Product	Yield (%)[b]	dr[c]
1	H	1	**4a**	95	>25:1
2	4-Cl	1	**4b**	96	>25:1
3	4-Br	1	**4c**	96	>25:1
4	5-Me	2	**4d**	93	>25:1
5	5-Cl	1	**4e**	95	>25:1
6	5-Br	1	**4f**	96	>25:1
7	5-NO_2	1	**4g**	99	>25:1
8	6-MeO	2	**4h**	92	>25:1
9	6-Br	1	**4i**	98	>25:1
10	7-Br	1	**4j**	97	>25:1
11[d]	H	24	**4k**	0	/
12[e]	H	24	**4l**	0	/

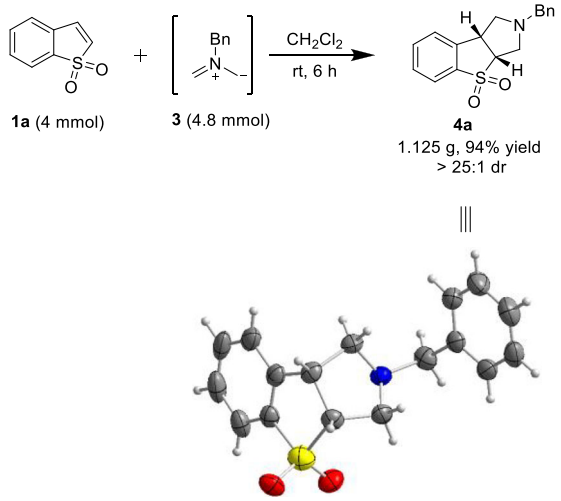
[a]Unless noted otherwise, reactions were performed with **1** (0.1 mmol), **2** (0.12 mmol), and TFA (0.12 mmol) in solvent (1.0 mL) at room temperature, X = SO_2.
[b]Isolated yield.
[c]Determined by ^{1}H-NMR analysis.
[d]X = S.
[e]X = N-Ts, Ts = *p*-toluenesulfonyl.

nonstabilized azomethine ylide **3** to generate the corresponding products **4** (**4a–j**) with the anticipated efficiency, in high yields with excellent diastereoselectivities (>25:1 dr), regardless of the positions and electronic properties of substituents on the phenyl ring which exhibited an electron-withdrawing group on the benzene rings, produced better yields compared with those with an electron-donating group on the benzene rings. Moreover, when the substituents were changed to the electron-rich groups such as the methyl or methoxy group (**4d** and **4h**), the yields were decreased slightly with 93% and 92% yields, respectively. It should be noted that the reactions did not occur when the substrate **1** was replaced by either benzo[*b*]thiophene or *N*-tosylindole under current reaction conditions, demonstrating that sulfone group at 1-position of benzo[*b*]thiophene

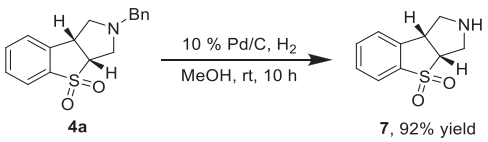
Scheme 1. 1,3-Dipolar [3 + 2] cycloaddition reaction of nonstabilized azomethine ylide **3** with the simpler acyclic aryl vinyl sulfone **5** under standard conditions.



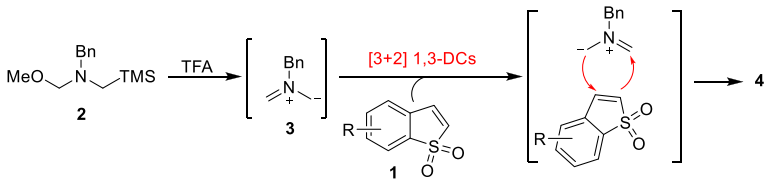
Scheme 2. Scaled-up version of 1,3-dipolar [3 + 2] cycloaddition reaction and X-ray single crystal structure of **4a**. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 3. Synthetic transformation of product **4a**.



Scheme 4. Plausible reaction mechanism. [Color figure can be viewed at wileyonlinelibrary.com]



ring as the electron-withdrawing group being required for this [3 + 2] annulation reaction to proceed under these conditions.

On the other hand, we have further explored the [3 + 2] dipolar cycloadditon of nonstabilized azomethine ylide **3** with the simpler acyclic aryl vinyl sulfone **5** under standard conditions and found that acyclic aryl vinyl sulfone **5a** and **5b** could also undergo this annulation reaction smoothly to give the corresponding cycloadduct **6a** [11a] and **6b** [11b] in 92% and 93% isolated yields, respectively, (Scheme 1) that the NMR data of the compounds were accordance with reported in literature.

Moreover, a gram scale experiment between 4 mmol of benzo[*b*]thiophene 1,1-dioxide **1a** and 4.8 mmol of nonstabilized azomethine ylide **3** proceeded smoothly under the optimized conditions and provided compound **4a** (1.125 g) in 94% yield (Scheme 2). Therefore, the present protocol was amenable to larger scale production. On the other hand, the benzyl group in **4a** can be easily removed by Pd/C-catalyzed hydrogenation to give the product **7** in 92% yield (Scheme 3).

On the basis of the experimental results and the previous studies, a plausible mechanism was proposed as illustrated in Scheme 4. Under standard conditions, *N*-benzyl-substituted compound **2** reacts with TFA to form the *in situ*-generated azomethine ylide intermediate **3**. Then, azomethine ylide intermediate **3** reacts with the benzo[*b*] thiophene sulfones **1** to generate the final product **4** through a [3 + 2] 1,3-DCs reaction.

CONCLUSIONS

In summary, we have developed an efficient synthesis of tricyclic pyrrolidine-fused benzo[*b*]thiophene 1,1-dioxide derivatives from the 1,3-dipolar [3 + 2] cycloaddition reaction between nonstabilized azomethine ylides generated *in situ* with benzo[*b*]thiophene 1,1-dioxides as the dipolarophiles, affording the desired products in high yields with excellent diastereoselectivities (up to 99% yield, >25:1 dr). In addition, the reaction could be scaled up to a gram scale without loss of selectivity. Further studies will be focused on exploring the asymmetric version of [3 + 2] cycloadditon reactions of nonstabilized azomethine ylides with dipolarophiles.

EXPERIMENTAL

NMR data were obtained for ^{1}H at 400 MHz and for ^{13}C at 100 MHz. Chemical shifts were given in parts per million (δ) from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. ESI HRMS was recorded on a Waters SYNAPT G2. Column chromatography was performed on silica gel (200–300 mesh) eluting with ethyl acetate and petroleum ether. Thin-layer chromatography was performed on glass-backed silica plates. UV light, I_2, and solution of potassium permanganate were used to visualize products. All chemicals were used without purification as commercially available unless otherwise noted. Petroleum ether and ethyl acetate (EtOAc) were distilled. Tetrahydrofuran was freshly distilled from sodium/benzophenone. Unless otherwise noted, experiments involving moisture and/or air sensitive components were performed under a positive pressure of argon in oven-dried glassware equipped with a rubber septum inlet. Dried solvents and liquid reagents were transferred by oven-dried syringes. Benzo[*b*]thiophene 1,1-dioxide compounds **1** [12] and acyclic aryl vinyl sulfone **5** [13] were prepared according to the literature procedures, respectively.

General procedure and characterizations data of compounds. To a solution of *N*-benzyl-*N*-(methoxy methyl)-*N*-trimethylsilylmethylamine **2** (0.12 mmol), benzo[*b*]thiophene 1,1-dioxide compounds **1** (0.1 mmol), or acyclic aryl vinyl sulfone **5** (0.1 mmol), respectively, in CH_2Cl_2 (1 mL) was added TFA (0.12 mol). The solution was stirred at room temperature for 1–2 h. After completion, product **4** or **6** was obtained by flash chromatography on silica gel (petroleum ether/ethyl acetate = 6:1 to 4:1).

(3aR,8bR)-2-benzyl-2,3,3a,8b-tetrahydro-1H-benzo[4,5] thieno[2,3-c]pyrrole 4,4-dioxide (4a). 28.4 mg, 95% yield, white solid; m.p. 152.5–154.2°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.28–7.22 (m, 3H), 7.17 (d, *J* = 6.4 Hz, 2H), 4.16–4.12 (m, 1H), 3.88 (td, *J* = 8.0, 2.8 Hz, 1H), 3.62 (s, 2H), 3.58 (dd, *J* = 10.8, 2.4 Hz, 1H), 2.95 (dd, *J* = 9.2, 2.8 Hz, 1H), 2.82–2.72 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.6, 139.6, 137.5, 133.8, 129.0, 128.4, 128.3, 127.2, 126.3, 121.3, 62.4, 60.1, 58.3, 54.3, 44.4.

ESI-HRMS: calcd for $C_{17}H_{17}NO_2S + Na^+$ 322.0872, found 322.0875.

(3aR,8bR)-2-benzyl-8-chloro-2,3,3a,8b-tetrahydro-1H-benzo[4,5]thieno[2,3-c]pyrrole 4,4-dioxide (4b). 32.0 mg, 96% yield, white solid; m.p. 172.1–173.4°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.31–7.27 (m, 2H), 7.25–7.23 (m, 3H), 4.21 (td, *J* = 8.4, 3.2 Hz, 1H), 3.91–3.87 (m, 1H), 3.73 (d, *J* = 12.8 Hz, 1H), 3.59–3.51 (m, 2H), 3.03–3.00 (m, 1H), 2.97–2.93 (m, 1H), 2.74 (dd, *J* = 10.4, 7.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.6, 137.3, 136.7, 134.0, 132.8, 130.9, 128.5, 128.4, 127.3, 119.9, 62.6, 58.28, 58.23, 53.8, 43.9. ESI-HRMS: calcd for $C_{17}H_{16}ClNO_2S + H^+$ 334.0663, found 334.0661.

(3aR,8bR)-2-benzyl-8-bromo-2,3,3a,8b-tetrahydro-1H-benzo[4,5]thieno[2,3-c]pyrrole 4,4-dioxide (4c). 36.2 mg, 96% yield, white solid; m.p. 179.5–180.7°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.31–7.27 (m, 2H), 7.25–7.22 (m, 3H), 4.19–4.14 (m, 1H), 3.91–3.87 (m, 1H), 3.73 (d, *J* = 9.6 Hz, 1H), 3.59–3.53 (m, 2H), 3.05–2.96 (m, 2H), 2.75 (dd, *J* = 9.6, 7.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.6, 138.4, 137.3, 137.2, 131.0, 128.5, 128.4, 127.3, 122.2, 120.5, 62.6, 58.4, 58.2, 53.8, 45.6. ESI-HRMS: calcd for $C_{17}H_{16}BrNO_2S + H^+$ 378.0158, found 378.0156.

(3aR,8bR)-2-benzyl-7-methyl-2,3,3a,8b-tetrahydro-1H-benzo[4,5]thieno[2,3-c]pyrrole 4,4-dioxide (4d). 29.1 mg, 93% yield, white solid; m.p. 128.8–129.7°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 7.26–7.17 (m, 5H), 7.10 (s, 1H), 4.09–4.05 (m, 1H), 3.87–3.82 (m, 1H), 3.66–3.52 (m, 3H), 2.94–2.91 (m, 1H), 2.80–2.77 (m, 1H), 2.70 (dd, *J* = 10.4, 8.0 Hz, 1H), 2.41 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.8, 140.0, 137.6, 136.9, 130.1, 128.5, 128.3, 127.2, 126.6, 121.0, 62.7, 60.2, 58.4, 54.3, 44.3, 21.8. ESI-HRMS: calcd for $C_{18}H_{19}NO_2S + H^+$ 314.1209, found 314.1207.

(3aR,8bR)-2-benzyl-7-chloro-2,3,3a,8b-tetrahydro-1H-benzo[4,5]thieno[2,3-c]pyrrole 4,4-dioxide (4e). 31.6 mg, 95% yield, white solid; m.p. 164.9–166.1°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.32 (s, 1H), 7.29 (d, *J* = 6.8 Hz, 1H), 7.26–7.21 (m, 2H), 7.21–7.17 (m, 2H), 4.10 (t, *J* = 7.6 Hz, 1H), 3.88 (t, *J* = 8.0 Hz, 1H), 3.67–3.57 (m, 3H), 2.97 (d, *J* = 8.8 Hz, 1H), 2.78 (t, *J* = 7.6 Hz, 1H), 2.73–2.68 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.7, 140.1, 138.2, 137.3, 129.7, 128.42, 128.41, 127.3, 126.5, 122.6, 62.8, 59.9, 58.2, 54.2, 44.2. ESI-HRMS: calcd for $C_{17}H_{16}ClNO_2S + H^+$ 334.0663, found 334.0661.

(3aR,8bR)-2-benzyl-7-bromo-2,3,3a,8b-tetrahydro-1H-benzo[4,5]thieno[2,3-c]pyrrole 4,4-dioxide (4f). 36.2 mg, 96% yield, white solid; m.p. 169.6–169.9°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63–7.57 (m, 2H), 7.50 (s, 1H), 7.30–7.28 (m, 1H), 7.26–7.23 (m, 2H), 7.17 (d, *J* = 7.2 Hz, 2H), 4.10 (t, *J* = 7.2 Hz, 1H), 3.89–3.84 m, 1H), 3.67–3.56 (m, 3H), 2.98–2.96 (m, 1H), 2.80–2.76 (m, 1H), 2.72–2.67 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.8, 138.7, 137.3, 132.5, 129.6, 128.42, 128.41, 127.3, 122.7, 62.7, 60.0, 58.2, 54.2, 44.1. ESI-HRMS: calcd for $C_{17}H_{16}BrNO_2S + H^+$378.0158, found 378.0155.

(3aR,8bR)-2-benzyl-7-nitro-2,3,3a,8b-tetrahydro-1H-benzo[4,5]thieno[2,3-c]pyrrole 4,4-dioxide (4g). 34.1 mg, 99% yield, yellow solid; m.p. 182.3–183.7°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.4 Hz, 1H), 8.22 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.28–7.23 (m, 3H), 7.15 (d, *J* = 6.8 Hz, 2H), 4.22 (t, *J* = 7.6 Hz, 1H), 3.96 (t, *J* = 8.0 Hz, 1H), 3.68–3.58 (m, 3H), 3.08 (d, *J* = 9.2 Hz, 1H), 2.85–2.81 (m, 1H), 2.71–2.67 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 151.4, 144.9, 141.8, 137.0, 128.5, 128.4, 127.4, 124.5, 122.7, 121.9, 63.0, 60.1, 58.1, 54.3, 44.3. ESI-HRMS: calcd for $C_{17}H_{16}N_2O_4S + H^+$ 345.0904, found 345.0901.

(3aR,8bR)-2-benzyl-6-methoxy-2,3,3a,8b-tetrahydro-1H-benzo[4,5]thieno[2,3-c]pyrrole 4,4-dioxide (4h). 30.3 mg, 92% yield, yellow solid; m.p. 142.5–144.4°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26–7.23 (m, 2H), 7.21–7.16 (m, 4H), 7.12–7.10 (m, 2H), 4.04 (t, *J* = 6.8 Hz, 1H), 3.89–3.84 (m, 1H), 3.82 (s, 3H), 3.59 (s, 2H), 3.56 (dd, *J* = 9.6, 1.2 Hz, 1H), 2.90 (dd, *J* = 9.2, 1.6 Hz, 1H), 2.73–2.64 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.1, 140.2, 137.4, 131.3, 128.3, 128.2, 127.03, 127.00, 122.5, 103.0, 63.1, 60.0, 58.1, 55.6, 54.2, 43.5. ESI-HRMS: calcd for $C_{18}H_{19}NO_3S + H^+$ 330.1158, found 330.1155.

(3aR,8bR)-2-benzyl-6-bromo-2,3,3a,8b-tetrahydro-1H-benzo[4,5]thieno[2,3-c]pyrrole 4,4-dioxide (4i). 36.9 mg, 98% yield, white solid; m.p. 171.9–172.7°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.29–7.22 (m, 3H), 7.21–7.16 (m, 3H), 4.07 (t, *J* = 7.2 Hz, 1H), 3.90–3.86 (m, 1H), 3.61–3.58 (m, 3H), 2.94 (d, *J* = 9.2 Hz, 1H), 2.77–2.73 (m, 1H), 2.71–2.66 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.4, 138.6, 137.3, 137.0, 128.42, 128.39, 127.9, 127.3, 124.2, 122.7, 62.9, 60.0, 58.2, 54.3, 44.1. ESI-HRMS: calcd for $C_{17}H_{16}BrNO_2S + H^+$ 378.0158, found 378.0157.

(3aR,8bR)-2-benzyl-5-bromo-2,3,3a,8b-tetrahydro-1H-benzo[4,5]thieno[2,3-c]pyrrole 4,4-dioxide (4j). 36.6 mg, 97% yield, white solid; m.p. 185.5–186.4°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.28–7.22 (m, 4H), 7.18 (d, *J* = 7.2 Hz, 2H), 4.06 (t, *J* = 7.2 Hz, 1H), 3.92–3.87 (m, 1H), 3.65–3.62 (m, 3H), 2.97–2.95 (m, 1H), 2.78–2.74 (m, 1H), 2.70 (dd, *J* = 10.8, 7.6 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.9, 138.8, 137.3, 134.6, 133.2, 128.5, 128.4, 127.3, 125.4, 116.1, 63.3, 60.1, 58.3, 54.5, 43.4. ESI-HRMS: calcd for $C_{17}H_{16}BrNO_2S + H^+$ 378.0158, found 378.0157.

1-Benzyl-3-(phenylsulfonyl)pyrrolidine (6a). 27.7 mg, 92% yield, pale yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.24–7.21 (m, 2H), 7.19–7.15 (m, 3H), 3.71–3.64 (m, 1H), 3.53 (q, *J* = 12.8 Hz, 2H), 2.80 (d, *J* = 7.6 Hz, 2H), 2.66–2.61 (m, 1H), 2.49 (dd, *J* = 16.0, 7.6 Hz, 1H), 2. 27–2.19 (m, 1H), 2.08–1.98 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.4, 138.3, 133.8, 129.3, 128.7, 128.6, 128.4, 127.2, 62.6, 59.6, 53.8, 53.4, 25.9. ESI-HRMS: calcd for $C_{17}H_{19}NO_2S + H^+$ 302.1209, found 302.1206.

1-Benzyl-3-((4-chlorophenyl)sulfonyl)pyrrolidine (6b). 31.2 mg, 93% yield, pale yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.32–7.25 (m, 3H), 7.20 (d, *J* = 7.2 Hz, 2H), 3.76–3.68 (m, 1H), 3.58 (q, *J* = 13.2 Hz, 2H), 2.89–2.81 (m, 2H), 2.70–2.64 (m, 1H), 2.58 (dd, *J* = 16.0, 7.6 Hz, 1H), 2.31–2.22 (m, 1H), 2.17–2.07 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 140.5, 138.0, 136.7, 130.1, 129.5, 128.5, 128.3, 127.2, 62.7, 59.4, 53.7, 53.2, 25.8. ESI-HRMS: calcd for $C_{17}H_{18}ClNO_2S + H^+$ 336.0820, found 336.0815.

General procedure synthetic transformation of product 4a. To a solution of compound **4a** (0.5 mmol, 149.5 mg) in MeOH (5 mL) was added the Pd/C (5% wt Pd on carbon, 15 mg, 10 wt%), followed by degassing with H_2 for three times at room temperature, and the resultant mixture was then stirred under a balloon pressure of H_2 for 10 h until the reaction was completed as monitored by thin-layer chromatography analysis. Then, the reaction mixture was filtrated off through a celite pad. The filtrate was concentrated under vacuum, and the residue was purified by a flash column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to give the product **7** (96.1 mg, 92% yield) as a colorless oil.

(3aR,8bR)-2,3,3a,8b-tetrahydro-1H-benzo[4,5]thieno[2,3-c]pyrrole 4,4-dioxide (7). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65–7.59 (m, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 4.22–4.17 (m, 1H), 3.89–3.83 (m, 2H), 3.24–3.17 (m, 2H), 3.09 (dd, *J* = 13.6, 7.6 Hz, 1H), 1.82 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.8, 139.2, 134.3, 129.3, 126.8, 121.1, 64.5, 55.8, 50.0, 47.4. ESI-HRMS: calcd for $C_{10}H_{11}NO_2S + H^+$ 210.0583, found 210.0584.

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[10] CCDC 1851340 contains the supplementary crystallographic data for compound **4a**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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