Dynamic Covalent Chemistry of Disulfides Offers a Highly Efficient Synthesis of Diverse Benzofused Nitrogen−Sulfur Heterocycles in One Pot

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The thiol-disulfide dynamic interchange reaction mediated by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was extensively studied. By this synthetic method sulfides can be prepared successfully within seconds in high yields at room temperature from stable and readily available disulfides and an alkylating agent. The method was further demonstrated to efficiently produce benzofused nitrogen−sulfur heterocycles with high skeletal diversity in a one-pot process.

Introduction

Sulfur-containing organic compounds are widely present in natural products and drugs.[1] Benzofused nitrogen−sulfur heterocycles, such as zopolrestat,[2] diltiazem,[3] and quetiapine[4] for clinical treatments of diabetes, hypertension, and schizophrenia and depressive episodes, respectively, (Figure 1), comprise an important class of compounds. Sulfides are usually obtained by the reactions of a thiolate or thiol with an organic halide or a Michael acceptor. However, most thiols or thiophenols are readily oxidized to their corresponding disulfide.[5] The disulfide bond can be broken and a carbon−sulfur bond formed by reducing reagents,[6] transition metal reagents or catalysts,[5,7] strong bases (e.g., NaH),[8] and thiolates.[9] However, these methods all possess one or more of the following disadvantages, including prolonged reaction time, harsh reaction conditions, or the requirement for costly, air-sensitive, and toxic substances. Thus, new methods using more stable and simply prepared disulfides to synthesize sulfides or sulfur heterocycles are very attractive.

Reversible thiol-disulfide interconversion has been studied previously[10] and has numerous applications for screening disulfide-based catalysis,[11] assembly of stable β-sheet peptides,[12] molecular recognition through a host−guest communication,[13] producing covalent cages[14] and the synthesis of polyrotaxane networks.[15] We hypothesized that the thiol-disulfide interchange could selectively provide various thiolates in situ in the presence of a suitable base and that these could react further to directly generate sulfides and sulfur-containing heterocycles. Although the thiol-disulfide interchange reaction to give thiols which can be alkylated to give sulfides is well-known,[16] to the best of our knowledge, no reports on the formation of sulfur−carbon bonds through the thiol-disulfide interchange reactions in a single one-pot sequence exist.

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Herein, we disclose a new and highly efficient synthesis of benzofused nitrogen−sulfur heterocycles involving a tandem or a multistep process in a one-pot reaction, which first involves a thiol-disulfide interchange reaction initiated by DBU in situ to form sulfides and then a cyclization reaction.

Result and Discussion

We began our study with the reactions of aromatic disulfides **1** and alkyl halides **2**, using different bases. Without ethanethiol (EtSH), the reaction of disulfide **1a** with **2a** in the presence of DBU[8b] did not afford any product at room temperature (r.t.; Table 1, entry 1). However, the reaction did produce the target product in low yield at 100 °C for 15 h (Table 1, entry 2). The reaction conditions were optimized by using several organic bases or other reagents. Much to our delight, when EtSH was added to the reaction solution, the anticipated product was obtained immediately at room temperature (Table 1, entries 3−5). Other organic bases such as DABCO, triethylamine (TEA), and DMAP were investigated in the presence of EtSH (Table 1, entries 6−8). The most favorable conditions were determined to be 2.0 equivalents (equiv) of DBU and 2.0 equiv of EtSH in tetrahydrofuran (THF; Table 1, entry 3), which afforded a quantitative yield of sulfide **3a** as determined by LC-MS analysis, within a very short reaction time. However, when less than 2.0 equiv of either DBU or EtSH were used, the yield of **3a** was reduced greatly (entries 4−5). When other weaker bases such as DMAP, DABCO, or TEA were used, the yield of **3a** decreased (Table 1, entries 6−8). The reaction efficacy was further demonstrated by the reaction of **1a** with the Michael acceptor **4a** to afford sulfide **5a**. It is evident from Table 2 that a low loading of DBU from 3 to 0.05 equiv is still effective, although the reactivity was decreased (entries 2−4). Taking into account the reaction time and yield, 0.5 equiv of DBU to **1a** was selected as the best reaction conditions for the Michael addition reactions. The use of DBU alone (Table 2, entry 1) or TEA and EtSH (Table

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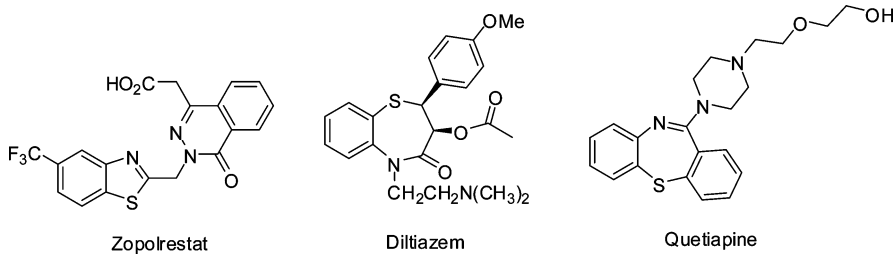
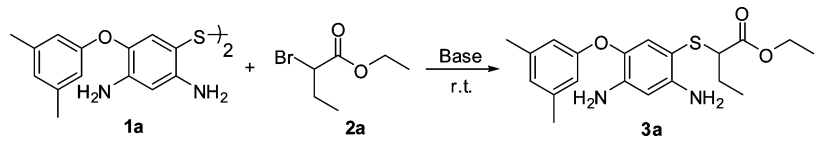


Figure 1. Bioactive Benzofused Sulfur Heterocycles.

Table 1. Nucleophilic Substitution Reactions Carried out under Basic Conditions[a]

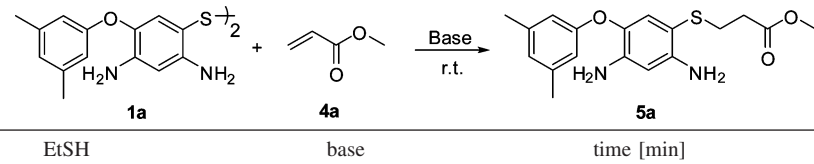


1a **2a** **3a**

entry	EtSH	base	time [min]	yield [%][b]
1	0	DBU (5 equiv)	300	0
2	0	DBU (5 equiv)	900	43[c]
3	2 equiv	DBU (2 equiv)	1	94[d]
4	2 equiv	DBU (1eq)	1	53[d]
5	1 equiv	DBU (2 equiv)	1	56[d]
6	3 equiv	DMAP (3 equiv)	300	49
7	3 equiv	DABCO (5 equiv)	300	52
8	3 equiv	TEA (5 equiv)	60	85

[a] **1a** (0.1 mmol) and **2a** (0.3 mmol) in 4 mL THF or MeOH at r.t. [b] Yield of Isolated product. [c] Reaction at 100 °C. [d] 0.2 mmol **2a** was used.

Table 2. Michael Addition Reactions Carried out under Basic Conditions



1a **4a** **5a**

entry	EtSH	base	time [min]	isolated yield [%]
1	0	DBU (5 equiv)	300	0
2	3 equiv	DBU (3 equiv)	1	92
3	3 equiv	DBU (0.5 equiv)	1	91
4	3 equiv	DBU (0.05 equiv)	180	72
5	3 equiv	TEA (5 equiv)	300	0

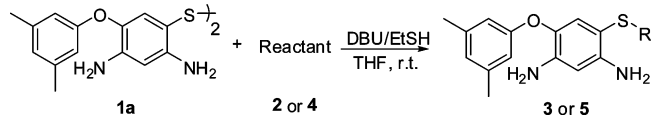
2, entry 5) did not produce the target product **5a**. We could conclude from the above reaction conditions that both DBU and EtSH were very important to the alkylation reaction and Michael addition reaction. Many organic solvents, such as THF, 1,4-dioxane, MeOH, DCM, and toluene, could be used in this reaction.

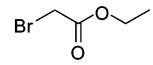
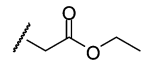
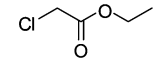
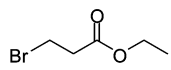
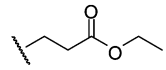
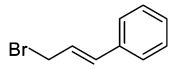
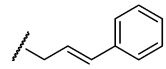
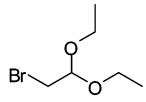
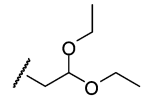
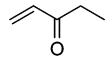
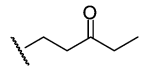
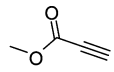
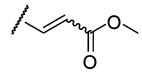
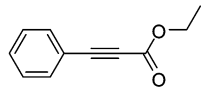
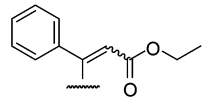
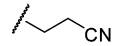
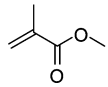
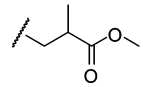
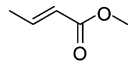
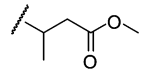
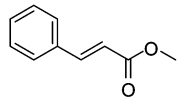
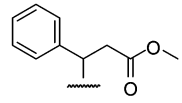
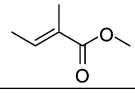
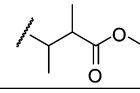
Using the optimal reaction conditions, a wide range of organic halides or Michael acceptors with various structures were investigated further. As is evident from Table 3, the reaction of α-halo esters and allylic bromides with **1a** readily afford the corresponding sulfides in high yields (entries 1, 2, 4). However, the yield of the product was reduced and stronger reaction condition needed to be used when the less reactive reagent α-bromo acetal was used (entry 5). Because of the steric effect and weaker reactivity of the reagent *t*-BuBr, the target product could not be obtained at all under the conditions examined (entry 6). Furthermore, the Michael adducts of **1a** were also efficiently obtained in good yields using a variety of α,*β*-unsaturated reagents (entries 7−12). However, the reactions with either α- or *β*-methyl substituted acrylates proceeded more slowly (entries 11−12). The reaction of **1a** with methyl cinnamate (entry 13) under the stronger reaction conditions afforded product in only low yield and methyl tiglate (entry 14) did not give the desired product because of weaker electrophilicity caused by a combination of steric and electronic effects. The *β*-bromo ester (entry 3) reacted well under standard conditions, but it is not clear if this is a direct alkylation or a base induced elimination-addition process.

The scope of this method was also demonstrated after extensively screening various aryl disulfides (Table 4). Most of the aryl disulfides with either electron-withdrawing or electron-donating groups gave quantitative reaction yields, as determined by LC-MS analysis, and isolated yields were also high (entries 1−8). Several functional groups, such as nitro, keto, and amido groups, are well-tolerated under these reaction conditions. These functional groups would allow additional transformations to give more complex sulfides or sulfur heterocycles. Disulfides also reacted with an α-halo ketone or benzoyl chloride to give sulfides or S-*p*-tolyl thiobenzoate, respectively, in very high yields (entries 9−10).

To elucidate the mechanism of the sulfide formation, the thiol-disulfide interchange process was monitored by ^{1}H NMR spectroscopy (Figure 2). The chemical shifts of TEA and EtSH did not change in a solution containing TEA and

Table 3. Organic Halides or Michael Acceptors that Were Reacted with Disulfide **1a** in the Presence of DBU/EtSH

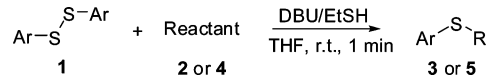


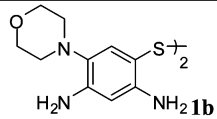
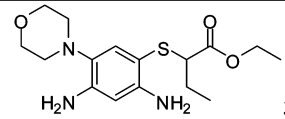
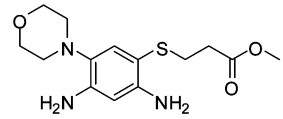
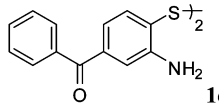
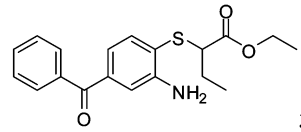
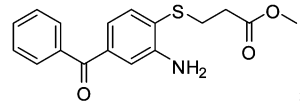
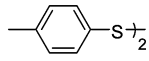
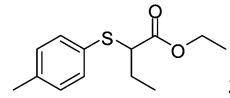
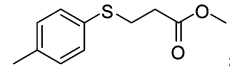
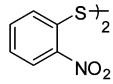
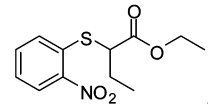
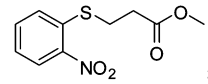
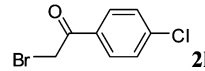
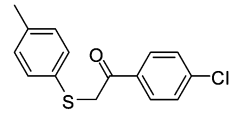
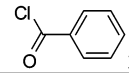
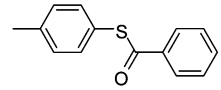
Entry	Reactant	Product (R =)	Time [min]	Isolated yield [%]
1[a]	 **2b**	 **3b**	1	90
2[a]	 **2c**	**3b**	1	95
3[a]	 **2d**	 **3c**	1	94
4[a]	 **2e**	 **3d**	1	96
5[b]	 **2f**	 **3e**	10	63
6[a]	 **2g**	 **3f**	300	0
7[c]	 **4b**	 **5b**	1	90
8[c]	 **4c**	 **5c** *E*/*Z* = 1:2	1	90
9[c]	 **4d**	 **5d** The ratio of two isomer = 4:1	1	88
10[c]	 **4e**	 **5e**	1	86
11[d]	 **4f**	 **5f**	60	78
12[d]	 **4g**	 **5g**	50	86
13[b]	 **4h**	 **5h**	20	59
14[d]	 **4i**	 **5i**	300	0

[a] Reaction conditions: **1a/2**/DBU/EtSH in molar ratio 1/3/3/3. [b] Reaction conditions: **1a/2** or **4**/DBU/EtSH in molar ratio 1/3/3 or 0.5/5, at 80 °C, assisted by Microwave. [c] Reaction conditions: **1a/4**/DBU/EtSH in molar ratio 1/3/0.5/3. [d] Reaction conditions: **1a/4**/DBU/EtSH in molar ratio 1/3/0.5/5.

EtSH (Figure 2 b, 2c). However, upon mixing of DBU and EtSH, the S−H proton signal disappeared and other proton signals were unaltered, which suggested that DBU could cause the thiol proton to be deuterated quickly (Figure 2 a−d). The ^{1}HNMR spectra (Figure 2, a−d) showed that neither TEA nor DBU could convert EtSH to a great amount of the corresponding EtS^-, and hence the ethanethiol reacted with α-bromo ester (**2a**) only very slowly to afford the byproduct of ethyl 2-(ethylthio)butanoate **3m** (Scheme 1). Furthermore, no change was detected in the presence of EtSH along with **1a** (Figure 2e). However, the new proton signals of **1f** and diethyl disulfide were clearly observed when DBU or TEA was added (Figure 2 f−i), which indicated that a thiol-disulfide dynamic exchange process occurred (Scheme 1). Considerable changes in the chemical shifts of protons 2, 6, 9, and 11 of DBU (the chemical shifts of DBU were assigned by 2D NMR in the Supporting Information) were observed, and DBU was demonstrated to be cationic ($DBU\cdot H^+$) in the thiol-disulfide interchange solution (Figure 2i). The aryl thiolate produced in situ by DBU reacted with organic halides very fast, and almost no byproduct (**3m**) (Scheme 1 and Table 1, entry 3) was produced. When TEA or another weaker base was used, a high concentration of the corresponding aryl thiolate was not produced, meaning that formation of **3a** was slow, and the byproduct (**3m** in Scheme 1) was produced in higher amounts, leading to

Table 4. Various Disulfides **1** Reacted with Organic Halides or Michael Acceptors



Entry	Disulfide	Reactant	Product	Isolated yield [%]
1[a]	 **1b**	**2a**	 **3g**	99
2[b]	**1b**	**4a**	 **5j**	98
3[a]	 **1c**	**2a**	 **3h**	86
4[b]	**1c**	**4a**	 **5k**	92
5[a]	 **1d**	**2a**	 **3i**	100
6[b]	**1d**	**4a**	 **5l**	98
7[a]	 **1e**	**2a**	 **3j**	95
8[b]	**1e**	**4a**	 **5m**	84
9[a]	**1d**	 **2h**	 **3k**	89
10[a]	**1d**	 **2i**	 **3l**	88

[a] Reaction conditions: **1a/2**/DBU/EtSH in molar ratio 1/3/3/3. [b] Reaction conditions: **1a/4**/DBU/EtSH in molar ratio 1/3/0.5/3.

reduced yields of the target product (Table 1, entries 6−8). The Michael adducts could be obtained using a catalytic amount of DBU, and the proposed mechanism is given in Scheme 2.

Having achieved a better understanding of the best conditions for synthesis of various sulfides, we expanded the method to prepare benzofused nitrogen−sulfur heterocycles in a one-pot process. Sulfur heterocycles (**6**, **7**, **8**) were obtained in good yields after the addition of DBU to a mixture of **1** and EtSH, and ethyl 2-chloro-3-oxobutanoate or isothiocyanate or CS_2 at room temperature, respectively, in a three-step tandem reaction involving aryl thiolate formation, nucleophilic addition (or nucleophilic substitution) and cyclization (Scheme 3, Table 5, entries 1−6). When **1** was reacted with α-halo esters in the presence of DBU and EtSH the sulfide intermediate formed immediately and was directly converted to **9** in a one-pot reaction under microwave conditions at 110 °C in 10 min (Scheme 4, Table 5, entries 7−14). The disulfides **1** reacted with α,β-unsaturated esters to yield the corresponding sulfides, which afforded the target compounds **10** and **11** in a one-pot reaction that involved an additional two-step reaction, involving hydrolysis with LiOH and cyclization with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC·HCl) (Scheme 4, Table 5, entries 15−18). Furthermore, the compounds of scaffolds **12** and **13** were obtained in a three-step, one-pot reaction, involving sulfide formation from the reaction of disulfide **1** with an α,β-unsaturated ketone or aldehyde or α-halo ketone, cyclization to a Schiff base and reduction with $NaBH_3CN$ (Scheme 4, Table 5, entries 19−22). Accordingly, a good variety of benzofused nitrogen−sulfur heterocycles with skeletal diversity could be prepared by this synthetic method.

Conclusion

In summary, we have reported an extensive study to establish a new and very efficient single-pot method to

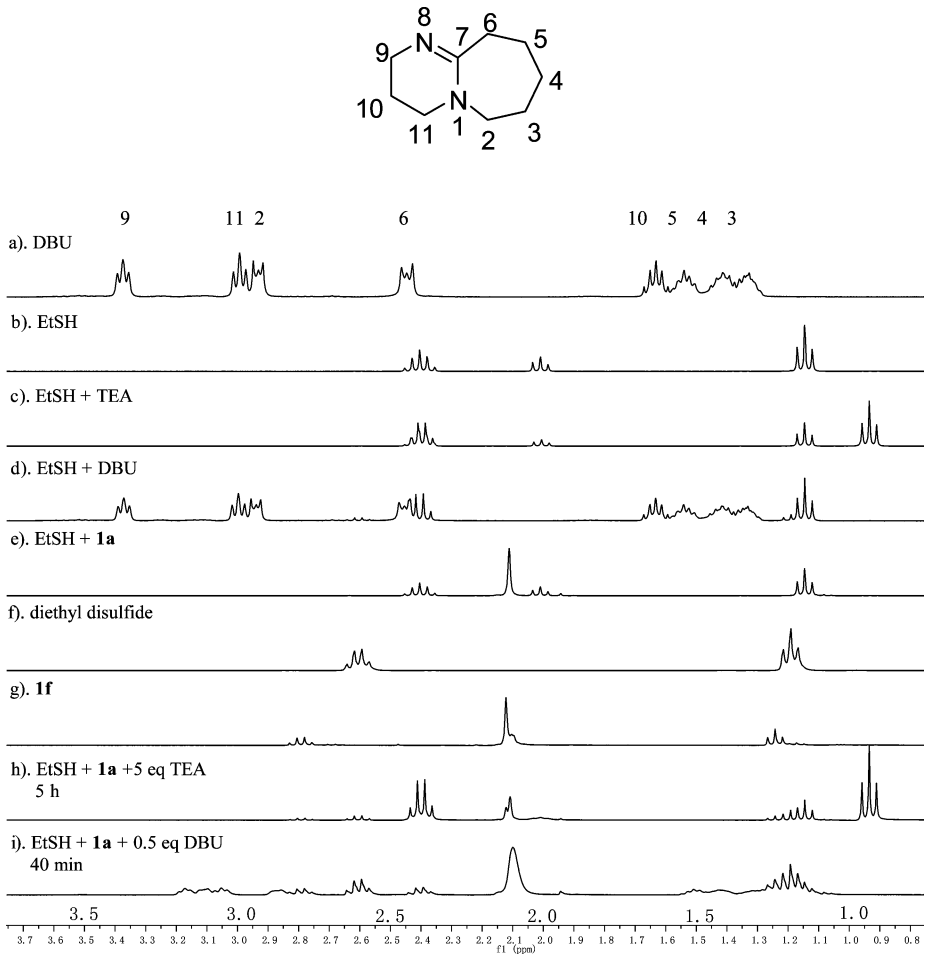
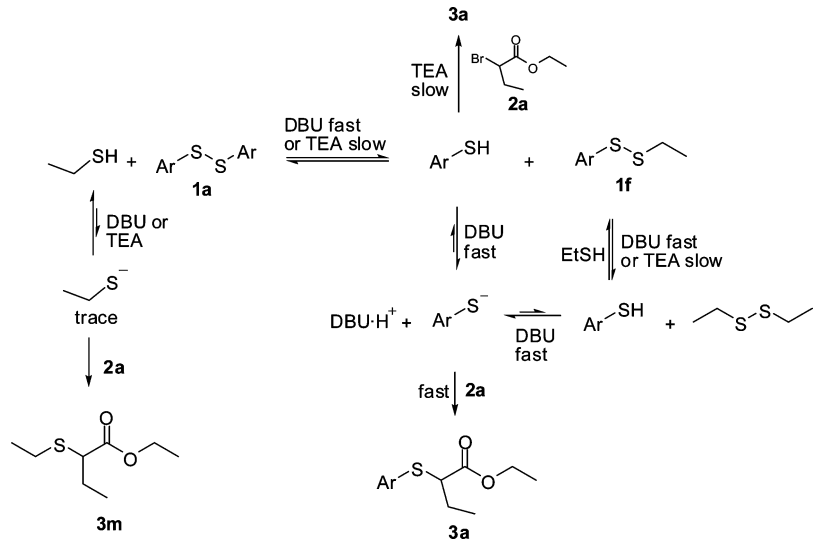


Figure 2. Dynamic Reversible Interchange of Disulfide **1a** and EtSH in the Presence of DBU or TEA as Determined by ^{1}H NMR Spectroscopy (300 MHz, C_5D_5N, 24 °C).

Scheme 1. Proposed Mechanism of Sulfide Formation Mediated by DBU/EtSH

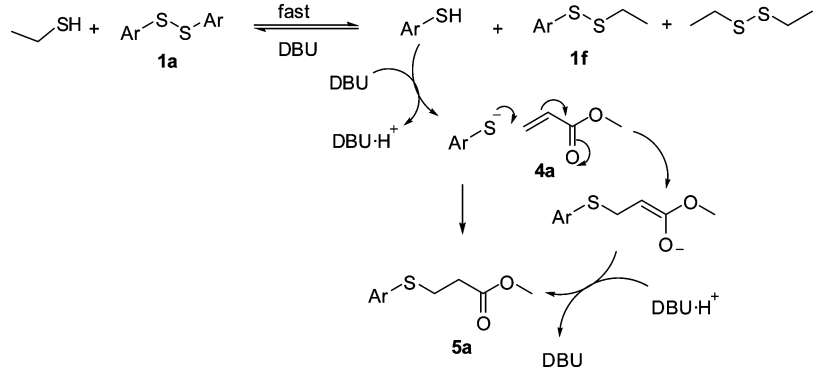


prepare diverse sulfides in high yields, via an in situ thiol-disulfide interchange reaction mediated by DBU. The methodology produced sulfides within seconds at room temperature from stable and readily available disulfides and a variety of alkylating agents. Our approach eliminates the requirements for hydride-based reducing agents or costly transition metal reagents or catalysts. We demonstrated the successful use of this synthetic method to efficiently prepare benzofused nitrogen−sulfur heterocycles with good skeletal diversity in a one-pot process.

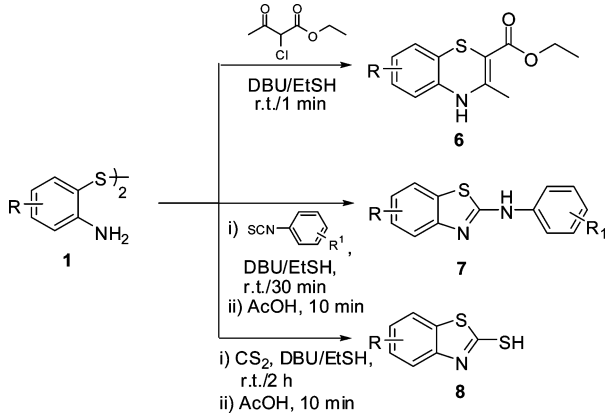
Experimental Section

General Procedure for the Synthesis of Sulfides 3. To a magnetically stirred solution of 1.0 equiv (0.1 mmol) of disulfide **1** in 4 mL of THF, 3.0 equiv of EtSH (0.3 mmol) and 3.0 equiv of DBU (0.3 mmol) were added, followed by

Scheme 2. Proposed Mechanism of Michael Addition Catalyzed by DBU



Scheme 3. Highly Efficient Synthesis of Benzofused Nitrogen−Sulfur Heterocycles in a Tandem Process



3.0 equiv of an organic halide **2** (α-halo esters, α-halo ketone, benzoyl chloride or allylic bromide) (0.30 mmol) at room temperature. The reaction mixture immediately produced a white solid upon addition of the alkyl halides, and disulfide **1** was completely consumed within 1 min as determined by LC-MS or TLC. Sulfides **3** could be isolated in excellent yield after purification by column chromatography through a silica gel column.

Ethyl 2-[2,4-Diamino-5-(3,5-dimethylphenoxy)phenylthio]butanoate, 3a. Isolated as a yellow oil (70 mg, 94%), (eluent: petroleum ether/ethyl acetate, 2/1, v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.88 (t, J = 7.3, 3H), 1.07 (t, J = 7.1, 3H), 1.52−1.79 (m, 2H), 2.19 (s, 6H), 3.26−3.34 (m, 1H), 3.96 (q, J = 7.1, 2H), 4.93 (s, 2H), 5.05 (s, 2H), 6.11 (s, 1H), 6.46 (s, 2H), 6.61 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.7, 13.9, 20.9, 24.1, 51.5, 60.3, 98.5, 99.9, 113.3, 123.2, 129.7, 132.3, 138.6, 143.5, 148.7, 158.6, 171.5. HRMS (ESI) Calcd. for $C_{20}H_{27}N_2O_3S$ [M + H]$^+$: 375.1742, Found: 375.1742.

General Procedure for the Synthesis of Sulfides 5. To a magnetically stirred solution of 1.0 equiv (0.1 mmol) of disulfide **1** in 4 mL of THF, 3.0 equiv of EtSH (0.3 mmol) and 0.5 equiv of DBU (0.05 mmol) were added, followed by 2.2 equiv of Michael acceptors such as propiolates, α,β-unsaturated ester, ketone, and nitrile (0.22 mmol) at room temperature. The reaction mixture immediately turned colorless upon addition of a Michael acceptor **4**, and disulfide **1** was completely consumed within 1 min as determined by LC-MS or TLC. Sulfides **5** could be achieved in excellent yields after purification by column chromatography through a silica gel column.

Methyl 3-[2,4-Diamino-5-(3,5-dimethylphenoxy)phenylthio]propanoate, 5a. Isolated as a colorless oil (63 mg, 91%), (eluent: petroleum ether/ethyl acetate, 1/1, v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (s, 6H), 2.45 (t, J = 7.2, 2H), 2.72 (t, J = 7.1, 2H), 3.54 (s, 3H), 4.86 (s, 2H), 5.06 (s, 2H), 6.14 (s, 1H), 6.45 (s, 2H), 6.61 (s, 1H), 6.67 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 20.9, 29.5, 33.5, 51.3, 100.0, 100.2, 113.2, 123.1, 129.2, 132.2, 138.7, 143.0, 148.1, 158.7, 171.9. HRMS (ESI) Calcd. for $C_{18}H_{23}N_2O_3S$ [M + H]$^+$: 347.1429, Found: 347.1431.

Synthesis of 6a by a Three-Step Tandem Reaction. To a magnetically stirred solution of 1.0 equiv (51.8 mg, 0.1 mmol) of disulfide **1a** in 4 mL of THF, 3.0 equiv of EtSH (0.3 mmol) and 2.2 equiv of ethyl 2-chloro-3-oxobutanoate (0.22 mmol) were added. Upon addition of 3.0 equiv of DBU (0.3 mmol) to the mixture solution at room temperature, disulfide **1a** was completely consumed within 1 min as determined by LC-MS or TLC. The reaction solution was evaporated under vacuum to dryness. Purification of the residue by column chromatography through a silica gel column eluting with petroleum ether and ethyl acetate (2:1, v:v) gave the compound **6a** as yellow solid, mp 134−135 °C (46 mg, 62%).

Ethyl 6-Amino-7-(3,5-dimethylphenoxy)-3-methyl-4*H*-benzo[*b*][1,4]thiazine-2-carboxylate, 6a. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.15 (t, J = 6.9, 3H), 2.20 (s, 9H), 4.01 (q, J = 6.9, 2H), 4.85 (s, 2H), 6.18 (s, 1H), 6.26 (s, 1H), 6.46 (s, 2H), 6.64 (s, 1H), 8.59 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.6, 20.2, 21.3, 60.0, 86.4, 103.2, 104.7, 114.0, 118.7, 124.1, 136.9, 138.2, 139.3, 139.9, 153.6, 158.0, 163.9. HRMS (ESI) Calcd. for $C_{20}H_{22}N_2O_3S$ [M]$^+$: 370.1351, Found: 370.1359.

Synthesis of 7 or 8 by a Three-Step Tandem Reaction. To a magnetically stirred solution of 1.0 equiv (0.1 mmol) of disulfide **1** in 4 mL of THF, 3.0 equiv of EtSH (0.3 mmol) and 3.0 equiv of isothiocyanate (0.3 mmol) or CS_2 (0.3 mmol) were added, followed by 3.0 equiv of DBU (0.3 mmol). The mixture was allowed to stir for an additional 30 min (isothiocyanate) or 2 h (CS_2) at room temperature and disulfide **1** was completely consumed as determined by LC-MS or TLC. After acidification with acetic acid (40 μL), the reaction solution was stirred for 10 min then evaporated under vacuum to dryness. The residue was purified by

column chromatography through a silica gel column gave the compounds **7** or **8**.

[2-(4-Methoxyphenylamino)benzo[*d*]thiazol-5-yl](phenyl) Methanone, 7b. Isolated as a white solid, mp 207−208 °C (67 mg, 93%), (eluent: dichloromethane/methanol, 100/1, v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.73 (s, 3H), 6.95 (d, J = 9.1, 2H), 7.51 (dd, J = 8.2, 1.6, 1H), 7.57 (t, J = 7.4, 2H), 7.63−7.73 (m, 3H), 7.73−7.80 (m, 3H), 7.96 (d, J = 8.1, 1H), 10.46 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 55.2, 114.2, 119.7, 119.9, 121.2, 123.1, 128.5, 129.5, 132.37, 133.6, 134.8, 135.3, 137.5, 152.2, 154.9, 163.1, 195.5. HRMS (ESI) Calcd. for $C_{21}H_{17}N_2O_2S$ [M + H]$^+$: 361.1011, Found: 361.1017.

5-Amino-6-morpholinobenzo[*d*]thiazole-2-thiol, 8b. Isolated as a yellow solid, mp 274−275 °C (48 mg, 90%), (eluent: petroleum ether/ethyl acetate, 4/1, v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.76 (t, J = 4.2, 4H), 3.74 (t, J = 4.2, 4H), 5.23 (s, 2H), 6.69 (s, 1H), 7.20 (s, 1H), 13.31 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 51.2, 66.5, 97.0, 112.4, 115.7, 136.5, 138.4, 142.9, 188.7. HRMS (ESI) Calcd. for $C_{11}H_{14}N_3OS_2$ [M + H]$^+$: 268.0578, Found: 268.0580.

Synthesis of 9 in a One-Pot Reaction. To a magnetically stirred solution of 1.0 equiv (0.1 mmol) of disulfide **1** in 4 mL of THF, 3.0 equiv of EtSH (0.3 mmol) and 3.0 equiv of DBU (0.3 mmol) were added, followed by 2.2 equiv of an α-halo ester (0.22 mmol) at room temperature. After disulfide **1** was completely consumed as determined by LC-MS or TLC (within 1 min), 200 μL AcOH was added directly to the reaction mixture. Then the mixture solution was irradiated in a Microwave oven at 110 °C for 10 min. After the solvent was evaporated under vacuum to dryness, the residue was purified by column chromatography through a silica gel column gave the desired products **9** in excellent yields.

6-Amino-7-(3,5-dimethylphenoxy)-2-ethyl-2*H*-benzo[*b*][1,4]-thiazin-3(4*H*)-one, 9a. Isolated as a white solid, mp 212−213 °C (63 mg, 96%), (eluent: petroleum ether/ethyl acetate, 1/1, v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (t, J = 7.3, 3H), 1.34−1.57 (m, 1H), 1.65−1.88 (m, 1H), 2.20 (s, 6H), 3.28 (dd, J = 8.5, 6.1, 1H), 5.00 (s, 2H), 6.44 (s, 1H), 6.48 (s, 2H), 6.67 (s, 2H), 10.32 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 11.2, 20.9, 22.2, 43.5, 102.7, 103.7, 114.1, 119.6, 123.9, 134.2, 137.4, 138.9, 140.0, 157.6, 167.1. HRMS (ESI) Calcd. for $C_{18}H_{21}N_2O_2S$ [M + H]$^+$: 329.1324, Found: 329.1329.

6-Benzoyl-2-ethyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one, 9g. Isolated as a white solid, mp 124−125 °C (53 mg, 89%), (eluent: petroleum ether/ethyl acetate, 3/1, v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.98 (t, J = 7.4, 3H), 1.42−1.66 (m, 1H), 1.70−1.93 (m, 1H), 3.57 (dd, J = 8.4, 6.2, 1H), 7.33 (dd, J = 8.0, 1.8, 1H), 7.41 (d, J = 1.7, 1H), 7.52 (d, J = 8.0, 1H), 7.54−7.62 (m, 2H), 7.64−7.77 (m, 3H), 10.74 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.1, 23.1, 42.7, 117.5, 123.7, 124.2, 127.8, 128.5, 129.5, 132.6, 135.2, 136.9, 137.0, 166.3,194.6. HRMS (ESI) Calcd. for $C_{17}H_{16}NO_2S$ [M + H]$^+$: 298.0902, Found: 298.0907.

Synthesis of 10 or 11 in a One-Pot Reaction. To a magnetically stirred solution of 1.0 equiv (0.1 mmol) of disulfide **1** in 4 mL of THF, 3.0 equiv of EtSH (0.3 mmol) and 0.5 equiv of DBU (0.05 mmol) were added, followed by 2.2 equiv of ethyl 3-phenylpropiolate or an α,β-unsaturated ester (0.22 mmol) at room temperature. The disulfide **1** was completely consumed within 1 min as determined by LC-MS or TLC. Then 6.0 equiv of LiOH·H_2O (0.6 mmol) in 2 mL of water was added directly to the stirred reaction solutions. The reaction mixture was continuously stirred for 30 min at room temperature (for α,β-unsaturated ester) or irradiated in a Microwave for 10 min at 90 °C (for ethyl 3-phenylpropiolate). After the hydrolysis of the ester by LiOH was complete as determined by LC-MS, the pH value of the reaction solution was adjusted to 7.0 with 2 N HCl. Then 4.0 equiv of EDC·HCl (0.4 mmol) was directly added to the reaction solution, and the mixture was allowed to react for an additional 30 to 60 min at 50 °C until the reaction was complete, as monitored by LC-MS or TLC. The mixture was concentrated under vacuum to remove THF and was extracted with DCM (3 × 50 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the products **10** or **11**.

7-Amino-8-(3,5-dimethylphenoxy)-2,3-dihydrobenzo[*b*][1,4]-thiazepin-4(5*H*)-one, 10a. Isolated as a white solid, mp 274−275 °C (47 mg, 75%), (eluent: dichloromethane/methanol, 25/1, v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.23 (s, 6H), 2.40 (t, J = 6.8, 2H), 3.22 (t, J = 6.9, 2H), 5.32 (s, 2H), 6.54 (s, 3H), 6.71 (s, 1H), 6.82 (s, 1H), 9.56 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 20.9, 33.5, 34.2, 109.6, 110.0, 114.7, 124.3, 125.5, 138.9, 139.0, 139.5, 141.9, 157.2, 172.5. HRMS (ESI) Calcd. for $C_{17}H_{19}N_2O_2S$ [M + H]$^+$: 315.1167, Found: 315.1166.

(*Z*)-7-amino-8-(3,5-dimethylphenoxy)-2-phenylbenzo[*b*][1,4]-thiazepin-4(5*H*)-one, 11a. Isolated as a light yellow solid, mp 207−208 °C (30.5 mg, 39%), (eluent: petroleum ether/ethyl acetate, 2/1, v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.21 (s, 6H), 5.37 (s, 2H), 6.47 (d, J = 1.2, 1H), 6.52 (s, 2H), 6.63 (s, 1H), 6.69 (s, 1H), 6.94 (s, 1H), 7.34−7.49 (m, 3H), 7.62−7.80 (m, 2H), 10.32 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 20.9, 108.6, 112.4, 114.4, 123.6, 124.2, 125.1, 127.3, 128.8, 129.9, 137.4, 138.6 139.0, 142.4, 149.5, 157.3, 167.6. HRMS (ESI) Calcd. for $C_{23}H_{21}N_2O_2S$ [M + H]$^+$: 389.1324, Found: 389.1323.

Synthesis of 12 or 13 in a One-Pot Reaction. To a magnetically stirred solution of 1.0 equiv (0.1 mmol) of disulfide **1** in 4 mL of THF, 3.0 equiv of EtSH (0.3 mmol) and 3.0 equiv of DBU (0.3 mmol, for α-halo ketone) or 0.5 equiv of DBU (0.05 mmol, for α,β-unsaturated ketone or aldehyde) were added, followed by 2.2 equiv of an α-halo ketone, α,β-unsaturated ketone or aldehyde (0.22 mmol) at room temperature. The disulfide **1** was completely converted into the unstable intermediate within 1 min as determined by LC-MS or TLC. After acidification with 6.0 equiv of acetic acid (0.6 mmol), 6.0 equiv of $NaBH_3CN$ (0.6 mmol) and 2 mL of MeOH were added directly to the stirred reaction solutions. The reaction mixture was continuously stirred for an additional 30 min at room temperature, and the unstable intermediates were completely converted into the stable target product **12** or **13** as monitored by LC-MS or TLC. After being quenched with saturated $NaHCO_3$ (0.5 mL), the reaction mixture was extracted with DCM (3 × 50

Table 5. Detailed Nitrogen−Sulfur Heterocycles Synthesized by This Method

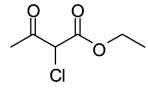
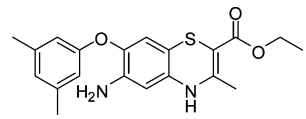
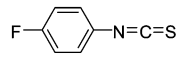
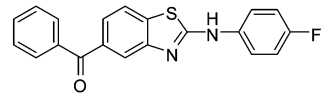
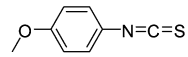
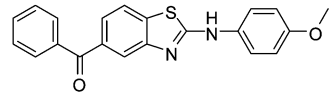
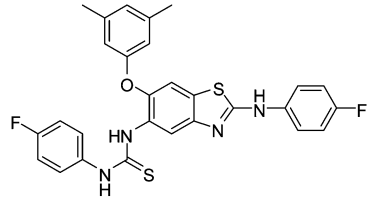
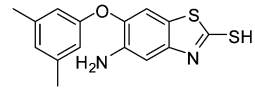
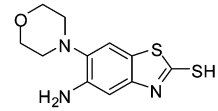
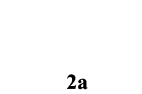
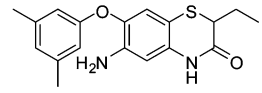
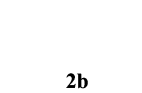
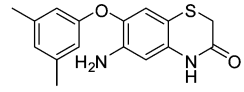
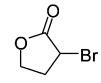
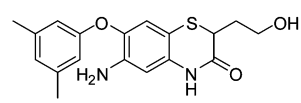
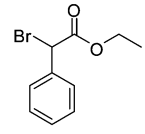
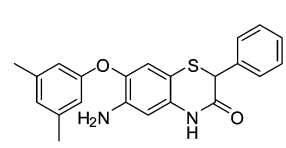
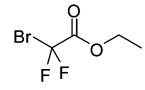
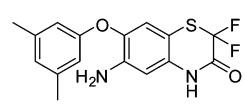
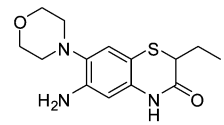
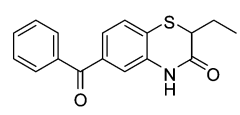
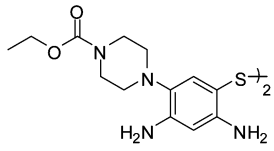
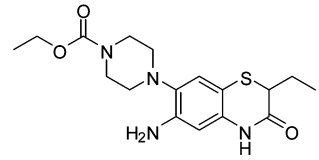
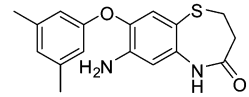
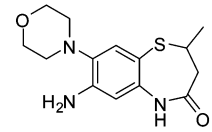
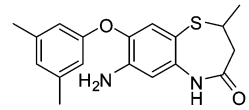
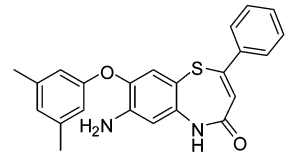
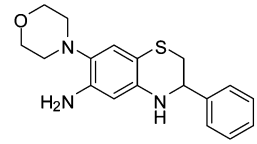
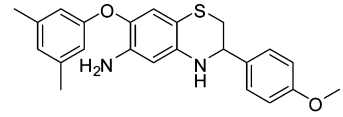
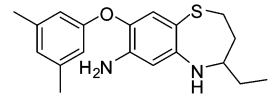
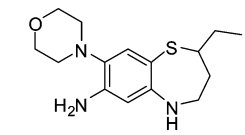
Entry	Disulfide	Reactant	Product	Isolated yield [%]
1	**1a**	 **2j**	 **6a**	62
2	**1d**	 **4j**	 **7a**	95
3	**1d**	 **4k**	 **7b**	93
4	**1a**	 **4j**	**7c**	75
5	**1a**	CS_2 **4l**	 **8a**	83
6	**1c**	**4l**	 **8b**	90
7	**1a**	 **2a**	 **9a**	96
8	**1a**	 **2b**	 **9b**	90
9	**1a**	 **2k**	 **9c**	95
10	**1a**	 **2l**	 **9d**	99
11	**1a**	 **2m**	 **9e**	73
12	**1c**	**2a**	 **9f**	99
13	**1d**	**2a**	 **9g**	89

Table 5. Continued

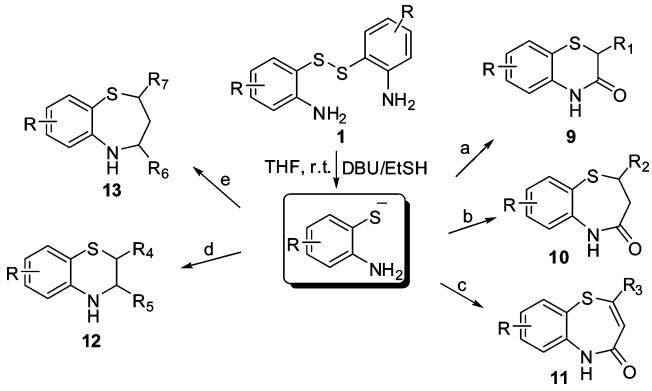
Entry	Disulfide	Reactant	Product	Isolated yield [%]
14	 **1g**	**2a**	 **9h**	92
15	**1a**	**4a**	 **10a**	75
16	**1c**	**4g**	 **10b**	50
17	**1a**	**4g**	 **10c**	57
18	**1a**	**4d**	 **11a**	39
19	**1c**	**2n**	 **12a**	77
20	**1a**	**2o**	 **12b**	66
21	**1a**	**4b**	 **13a**	92
22	**1c**	**4m**	 **13b**	65

mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the products **12** or **13**.

7-Morpholino-3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazin-6-amine, 12a. Isolated as a white solid, mp 217−218 °C (50 mg, 77%), (eluent: dichloromethane/methanol, 100/1, v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.58−2.75 (m, 4H), 2.82−3.04 (m, 2H), 3.61−3.77 (m, 4H), 4.50−4.68 (m, 3H), 5.99 (s, 1H), 6.08 (s, 1H), 6.45 (s, 1H), 7.28 (dt, J = 8.6, 4.2, 1H), 7.35 (d, J = 4.2, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 32.2, 51.8, 54.7, 66.8, 99.6, 101.1, 118.2, 126.7, 127.2, 128.2, 129.8, 139.8, 140.9, 144.2. HRMS (ESI) Calcd. for $C_{18}H_{22}N_3OS$ $[M + H]^+$: 328.1484, Found: 328.1484.

7-(3,5-Dimethylphenoxy)-3-(4-methoxyphenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazin-6-amine, 12b. Isolated as a colorless oil (52 mg, 66%), (eluent: petroleum ether/ethyl acetate, 3/1, v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20 (s, 6H), 2.91 (d, J = 5.4, 2H), 3.74 (s, 3H), 4.46 (s, 2H), 4.54 (t, J = 4.9, 1H), 6.03 (s, 1H), 6.15 (s, 1H), 6.36 (s, 1H), 6.46 (s, 2H), 6.61 (s, 1H), 6.91 (d, J = 8.7, 2H), 7.29 (d, J = 8.6, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 21.0, 32.2, 54.3, 55.1, 100.0, 102.0, 113.4, 113.6, 119.3, 123.2,

Scheme 4. Highly Efficient Synthesis of Benzofused Nitrogen−Sulfur Heterocycles in a Multistep Process in One Pot[a]



[a] Reagents and conditions: (a) (i) α-halo ester, 1 min; (ii) AcOH, MW, 10 min; (b) (i) α,β-unsaturated ester, 1 min; (ii) LiOH, THF/H_2O, r.t., 30 min; (iii) HCl (aq.), EDC·HCl, r.t., 3 h; (c) (i) ethyl 3-phenylpropiolate, 1 min; (ii) LiOH, THF/H_2O, MW, 10 min; (iii) HCl (aq.), EDC·HCl, r.t., 3 h; (d) (i) α-halo ketone, 1 min; (ii) $NaBH_3CN$, AcOH, MeOH/THF, r.t., 20 min; (e) (i) α,β-unsaturated ketone or aldehyde, 1 min; (ii) $NaBH_3CN$, AcOH, MeOH/THF, r.t., 20 min.

127.9, 133.3, 135.8, 138.6, 138.7, 140.6, 158.6. HRMS (ESI) Calcd. for $C_{23}H_{25}N_2O_2S$ $[M + H]^+$: 393.1637, Found: 393.1639.

8-(3,5-Dimethylphenoxy)-4-ethyl-2,3,4,5-tetrahydrobenzo-[*b*][1,4]thiazepin-7-amine, 13a. Isolated as a white solid, mp 137−138 °C (60 mg, 92%), (eluent: petroleum ether/ethyl acetate, 2/1, v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (t, J = 7.3, 3H), 1.37−1.56 (m, 2H), 1.56−1.75 (m, 1H), 1.88−2.12 (m, 1H), 2.19 (s, 6H), 2.39−2.47 (m, 1H), 2.80−3.07 (m, 2H), 4.60 (s, 1H), 4.71 (s, 2H), 6.35 (s, 1H), 6.45 (s, 2H), 6.58 (s, 1H), 6.63 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 11.0, 21.0, 28.4, 30.4, 38.1, 57.9, 107.2, 110.2, 113.8, 123.5, 123.8, 134.9, 138.7, 140.0, 148.7, 158.1. HRMS (ESI) Calcd. for $C_{19}H_{25}N_2OS$ $[M + H]^+$: 329.1688, Found: 329.1691.

2-Ethyl-8-morpholino-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepin-7-amine, 13b. Isolated as a white crystal, mp 182−183 °C (38 mg, 66%), (eluent: dichloromethane/methanol, 100/1, v/v); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97 (t, J = 7.3, 3H), 1.49 (p, J = 7.1, 2H), 1.64 (m, 1H), 1.93−2.18 (m, 1H), 2.55−2.84 (m, 6H), 3.28 (m, 1H), 3.69 (s, 4H), 4.79 (s, 2H), 5.11 (s, 1H), 6.16 (s, 1H), 6.74 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 11.9, 27.5, 45.3, 46.9, 51.6, 66.7, 105.1, 108.0, 124.1, 131.1, 142.6, 150.7. HRMS (ESI) Calcd. for $C_{15}H_{24}N_3OS$ $[M + H]^+$: 294.1640, Found: 294.1643.

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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