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Application of Thio-Ugi Adducts for the Preparation of Benzo[*b*]thiophene and S-Heterocycle Library via Copper Catalyzed Intramolecular C−S Bond Formation

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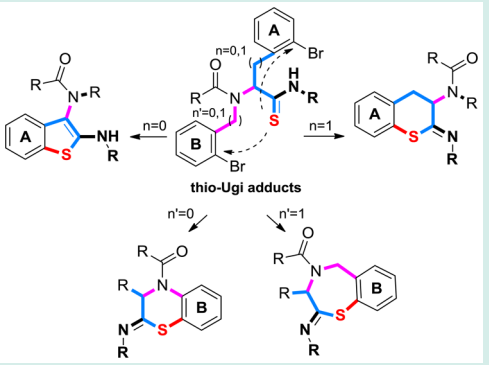
Supporting Information

ABSTRACT: Fused heterocycles, such as benzo[*b*]thiophene, thiochroman, benzo[*b*][1,4]thiazine, and 1,4-benzothiazepine were generated from thio-Ugi adducts containing a thioamide group through copper-catalyzed intramolecular C−S bond formation under microwave irradiation.



KEYWORDS: *thio-Ugi, copper, benzothiophene, thiochroman, benzothiazine, benzothiazepine*

INTRODUCTION

Various strategies have been harnessed to quickly and efficiently achieve the construction of chemical libraries for drug discovery. Among them, multicomponent reactions (MCRs) play a pivotal role in solution phase synthesis to easily and quickly generate a large number of compounds using simple starting materials.[1] The merits have driven many research groups to devise entirely novel MCRs. However, the accumulated MCRs released to date are not enough to fill chemical space with peculiar and unconventional compounds, which emphasizes the difficulty in designing new MCRs. Therefore, to complement existing MCRs, variations of them and either further transformations[2,3] or pairing strategies[4] after conducting MCRs have been continuously reported.

The Ugi reaction is a four-components reaction that incorporates an aldehyde or ketone, an isocyanide, an amine and a carboxylic acid or thioacid.[5] Generally, the Ugi adduct obtained from the reaction is more popular as the substrate for rendering new scaffolds because they could not be easily accessed from other routes in many cases. Diverse heterocycles have been generated via the adducts in combination with either classical protocols[2] or transition metal catalyzed reactions.[3]

Synthetic efforts toward the synthesis of heterocycles via intramolecular C−S bond formation, emerged by development of catalysts and ligands, have mainly focused on thiazoles fused with aryls, such as benzene,[3b,6] pyridine,[6b] pyrimidine,[7] pyridazine,[8] and pyrazine.[9] As far as we know, application of the transformation is rare with other heterocycles containing a sulfur atom and even with the prominent bicyclic core

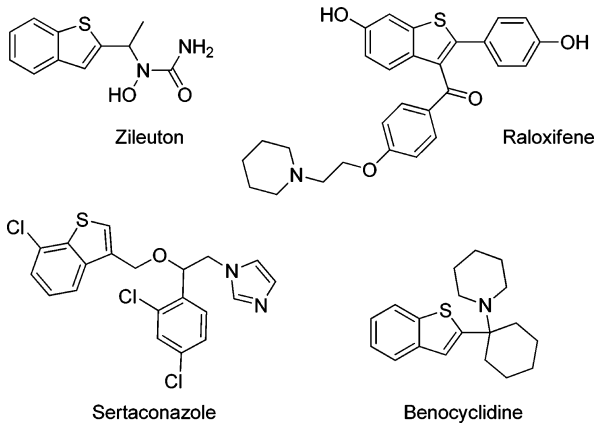


Figure 1. Examples of bioactive molecules containing benzo[*b*]-thiophenes.

benzo[*b*]thiophene found in biologically active compounds (Figure 1).[10] For the purpose of library production, we envisioned that the Ugi adducts **5** containing a thioamide could be elegant substrates for the study of intramolecular C−S coupling reactions to produce the fused heterocyclic compounds **8**−**11** (Scheme 1). In this report, we will discuss the synthesis of these heterocycles.

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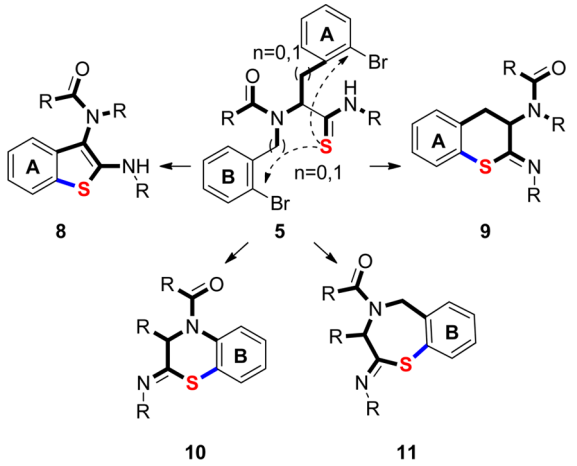
Scheme 1. Synthetic Strategy for Heterocycles from Thio-Ugi Adducts

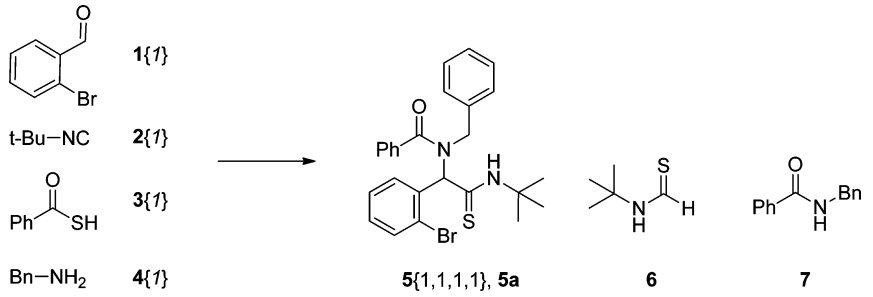


RESULTS AND DISCUSSION

Initially, we conducted Ugi reactions in methanol and identified that there were two other products **6**[11] and **7** with the desired product **5a**; the two byproducts had not been reported in papers pertinent to thio-Ugi synthesis (Table 1).[2b,e,h,3b] By substitution of methanol with 2,2,2-trifluororoethanol (TFE), the yield of **5a** significantly increased while that of the two byproducts declined. A more acidic character of TFE than methanol seemed to drive the formation of the adduct. We speculated that water emanating from imine formation could be responsible for the undesired products and partly succeeded in reducing them with drying agents.[3a,12] But we did not use $MgSO_4$, because it did not always afford positive results in yields with other amines. Also, the isolation of Ugi adducts in the absence of $MgSO_4$ was more convenient when the product precipitated in the reaction mixture.

The C−S bond formation from **5a** was achieved without the aid of transition metals, such as palladium or copper, as reported

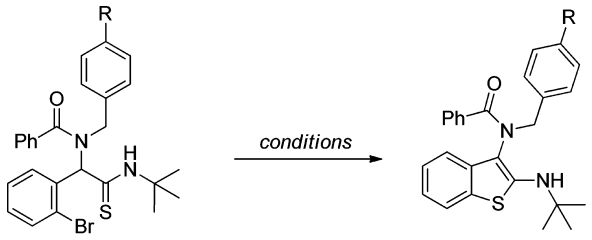
Table 1. Optimization of Thio-Ugi Reaction[a]



entry	solvent	addictive	yields (%)[b] 5	6	7
1	MeOH		25	21	48
2	TFE		63	9	23
3	TFE	$MgSO_4$ (1 equiv)	65	trace	16
4	TFE	Molecular sieve (4 Å)	50	trace	10

[a]Reaction conditions: **1**{*1*} (1 mmol), **2**{*1*} (1 equiv), **3**{*1*} (1 equiv), **4**{*1*} (1 equiv), and solvent (2 mL) under at 25 °C. [b]Isolated yield.

Table 2. Optimization for C−S Bond Formation[a]



5a (R = H)
5b (R = Cl)

8a (R = H)
8b (R = Cl)

entry	R	cat. (mol %)	ligand (mol %)	base	solvent	temp (°C)/time (h)	yield (**5**/**8**) (%)[b]
1	H			Cs_2CO_3	toluene	110/1	-/90
2	Cl			Cs_2CO_3	Toluene	110/12	trace
3	Cl			K_3PO_4	Toluene	110/20	50/44
4	Cl	CuI (10)		K_3PO_4	toluene	110/6	45/33
5	Cl	CuI (10)	1,10-phen (10)	K_3PO_4	THF	80/4	31/50
6	Cl	CuI (20)	1,10-phen (20)	K_3PO_4	THF	80/3	-/80
7	Cl	CuI (20)	1,10-phen (20)	K_3PO_4	THF (MW)	100/1	56/42
8	Cl	CuI (20)	1,10-phen (20)	K_3PO_4	THF/water (MW)[c]	100/1	-/94
9	Cl	CuI (20)	1,10-phen (20)	K_3PO_4	THF/water[c]	80/6	70

[a]Reaction conditions: **5** (0.4 mmol), base (2 equiv). [b]Isolated yield. [c]THF (4.75 mL) and water (0.25 mL).

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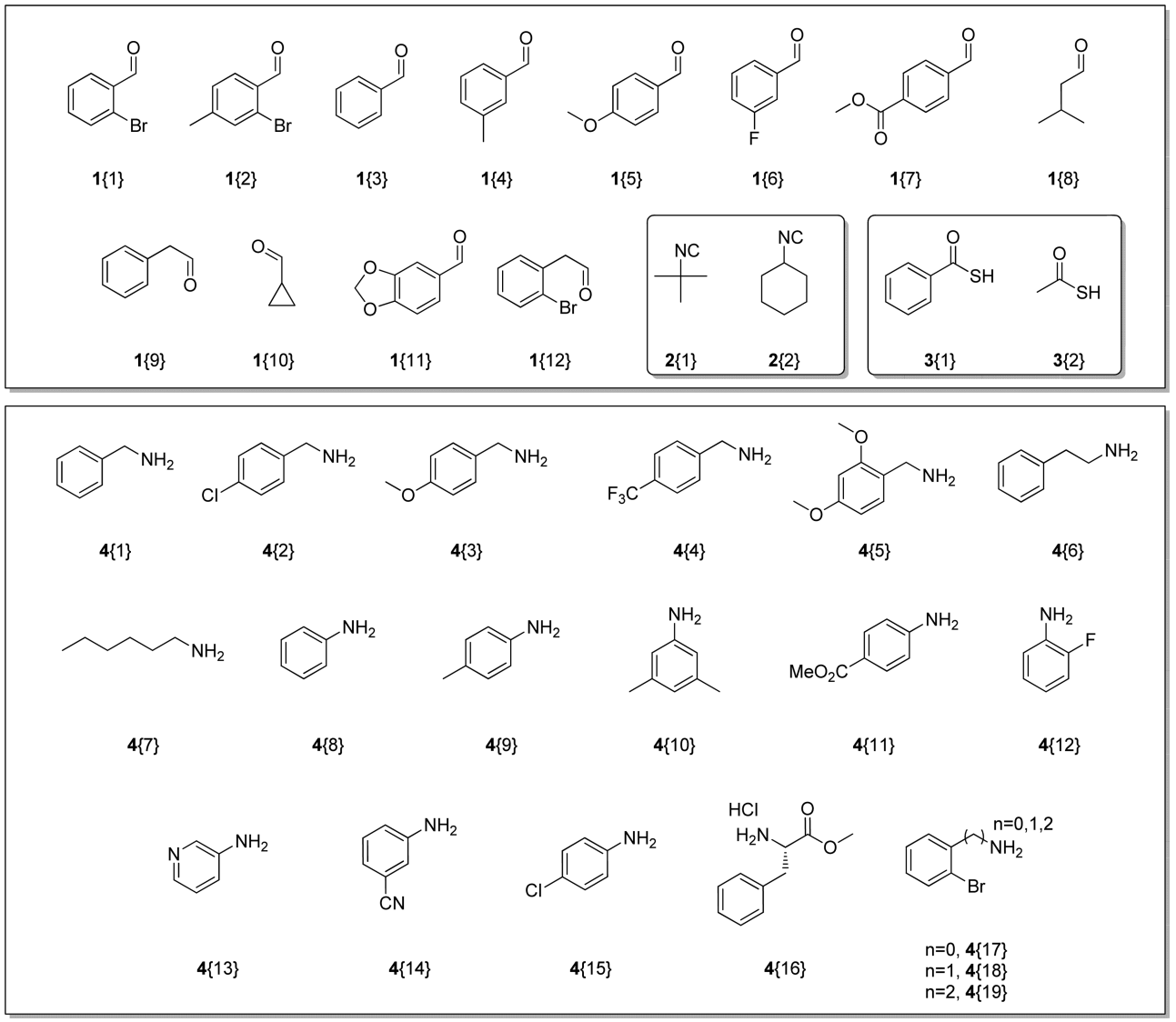

Figure 2. A list of four components used for thio-Ugi reaction.

by Liu et al.[6f] Interestingly, we obtained the desired product with only Cs_2CO_3 (Table 2, entry 1). However, when implementing the Cs_2CO_3 conditions with other substrates, the yield of **8** was not satisfactory despite prolonged reaction times. Therefore, we changed the model compound **5a** to **5b** which was almost unreactive under the Cs_2CO_3 conditions (Table 2, entry 2). Addition of copper iodide and 1,10-phenanthroline (1,10-phen) was effective in completing the reaction (Table 2, entry 6). To reduce the reaction time, microwave irradiation (MW) was introduced, which tends to give better yields in a shorter time than conventional heating. It is noteworthy that while microwave heating afforded no benefits with only THF (Table 2, entry 7), the addition of water to the THF resulted in excellent yields (Table 2, entry 8).

A range of amines **1**, two types of isocyanides **2** and thioacids **3**, as well as various aldehydes **4** were used to prepare thio-Ugi adducts **5**, which were subsequently transformed into fused cyclic derivatives **8**−**11**. The confirmation of thio-Ugi adducts synthesized with thiobenzoic acid **3**{*1*} was accomplished by NMR and LC/MS. However, structure elucidation of adducts from thioacetic acid **3**{*2*} was difficult using NMR spectra due to the restricted C−N amide bond.[2c] Thus, purity and structural identification of the adducts were confirmed by LC/MS. Compared to the known yields of Ugi adducts with carboxylic acid, those of thio-Ugi adducts **5** with thioacids **3** tended to be lower. Although a limited number of thio-Ugi adducts **5** were prepared, we observed some evidence from the results (Tables 3 and 4) suggesting that the yields of thio-Ugi **5** are affected by both electronic and steric effects. The bar graphs are attached to illustrate and help with understanding the trends at a glance (Figure 3). Figure 3a and 3b show that amines bearing electron donating groups (EDG) are better than those with electron withdrawing groups (EWG), and also that alkyl amines are superior to aryl amines which is in accord with the former conclusion. From Figure 3c, it is clear that steric factors are closely related to the production of Ugi adducts.

With these thio-Ugi substrates in hand, we set out to prepare benzo[*b*]thiophenes **8** under the optimized condition described above (Table 3). During the process, no negative events arose and the yields of **8** were good to moderate. When the thio-Ugi adduct **5af** obtained from an optically pure amino ester **4**{*16*} was used, two inseparable (silica gel chromatography) tautomers **8af** and **8ag** were observed. However, the optical

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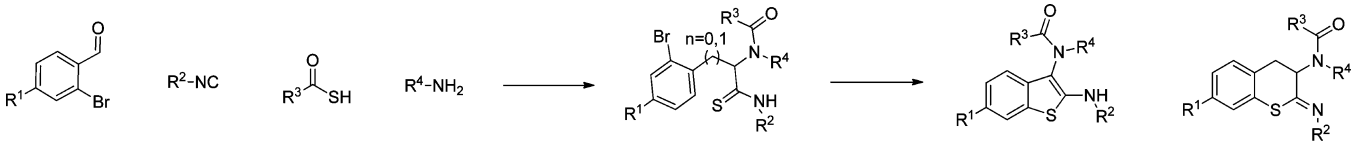
Table 3. Synthesis of Thio-Ugi Adducts and Their Corresponding Heterocycles



1{*1-2*} 2{*1-2*} 3{*1-2*} 4{*1-15*} 5 8 9

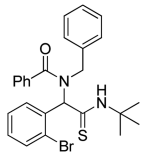
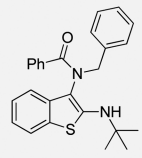
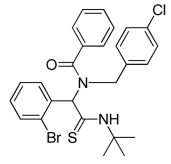
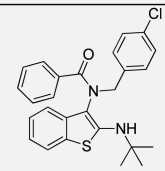
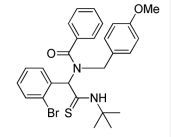
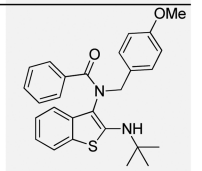
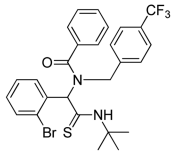
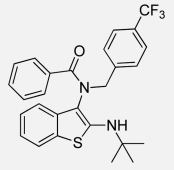
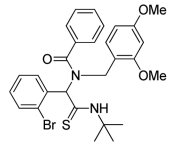
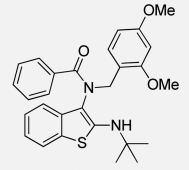
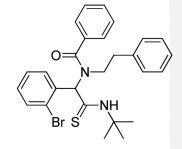
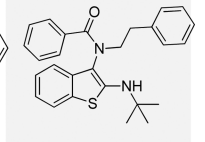
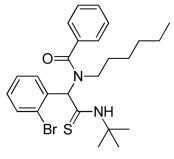
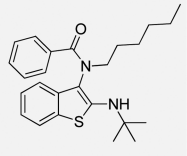
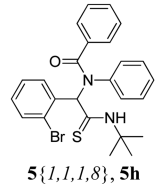
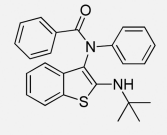
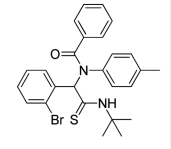
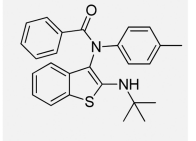
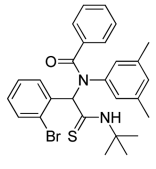
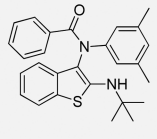
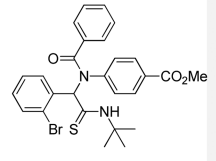
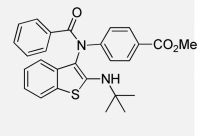
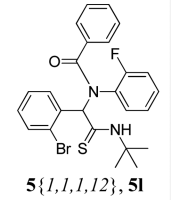
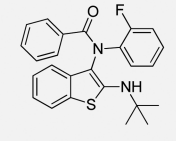
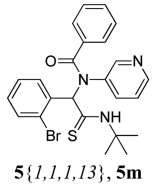
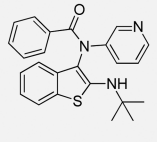
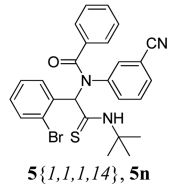
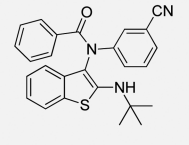
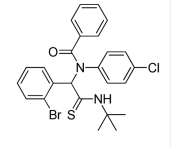
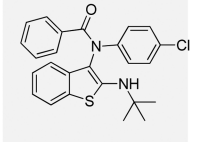
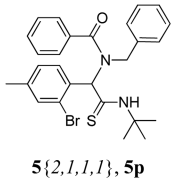
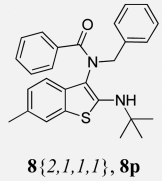
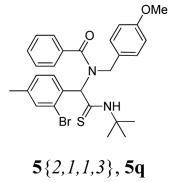
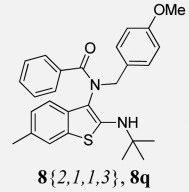
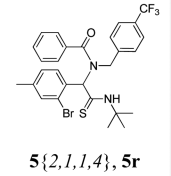
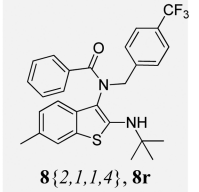
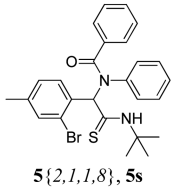
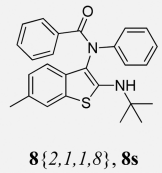
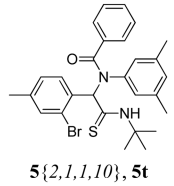
No	Ugi adducts[a,b]	Products[b,c]	No	Ugi adducts[a,b]	Products[b,c]	No	Ugi adducts[a,b]	Products[b,c]
1	 **5**{*1,1,1,1*}, **5a** 63%	 **8**{*1,1,1,1*}, **8a** 90%	2	 **5**{*1,1,1,2*}, **5b** 42%	 **8**{*1,1,1,2*}, **8b** 94%	3	 **5**{*1,1,1,3*}, **5c** 56%	 **8**{*1,1,1,3*}, **8c** 85%
4	 **5**{*1,1,1,4*}, **5d** 40%	 **8**{*1,1,1,4*}, **8d** 80%	5	 **5**{*1,1,1,5*}, **5e** 55%	 **8**{*1,1,1,5*}, **8e** 86%	6	 **5**{*1,1,1,6*}, **5f** 47%	 **8**{*1,1,1,6*}, **8f** 65%
7	 **5**{*1,1,1,7*}, **5g** 45%	 **8**{*1,1,1,7*}, **8g** 74%	8	 **5**{*1,1,1,8*}, **5h** 40%	 **8**{*1,1,1,8*}, **8h** 70%	9	 **5**{*1,1,1,9*}, **5i** 44%	 **8**{*1,1,1,9*}, **8i** 82%
10	 **5**{*1,1,1,11*}, **5j** 40%	 **8**{*1,1,1,10*}, **8j** 70%	11	 **5**{*1,1,1,11*}, **5k** 31%	 **8**{*1,1,1,11*}, **8k** 84%	12	 **5**{*1,1,1,12*}, **5l** 26%	 **8**{*1,1,1,12*}, **8l** 75%
13	 **5**{*1,1,1,13*}, **5m** 7%	 **8**{*1,1,1,13*}, **8m** 62%	14	 **5**{*1,1,1,14*}, **5n** 22%	 **8**{*1,1,1,14*}, **8n** 67%	15	 **5**{*1,1,1,15*}, **5o** 25%	 **8**{*1,1,1,15*}, **8o** 80%
16	 **5**{*2,1,1,1*}, **5p** 44%	 **8**{*2,1,1,1*}, **8p** 91%	17	 **5**{*2,1,1,3*}, **5q** 58%	 **8**{*2,1,1,3*}, **8q** 81%	18	 **5**{*2,1,1,4*}, **5r** 37%	 **8**{*2,1,1,4*}, **8r** 74%
19	 **5**{*2,1,1,8*}, **5s**	 **8**{*2,1,1,8*}, **8s**	20	 **5**{*2,1,1,10*}, **5t**	**8**{*2,1,1,10*}, **8t**	21	**5**{*1,2,1,1*},**5u**	**8**{*1,2,1,1*}, **8u**

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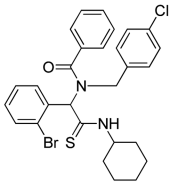
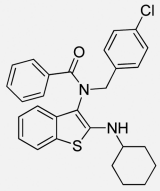
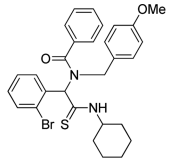
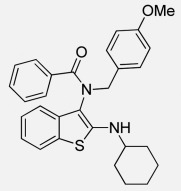
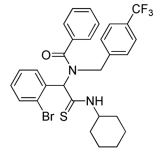
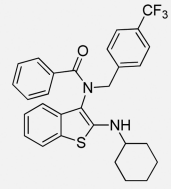
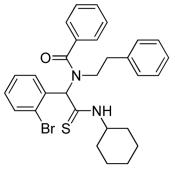
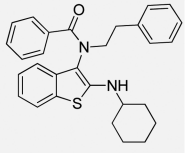
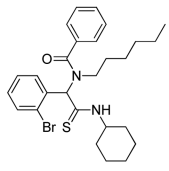
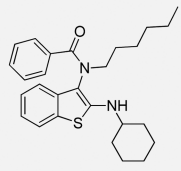
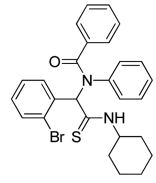
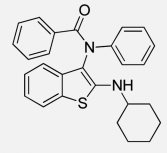
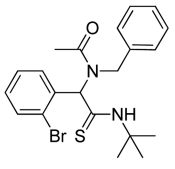
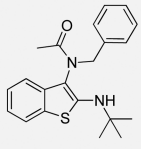
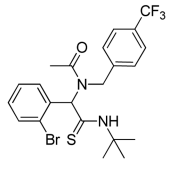
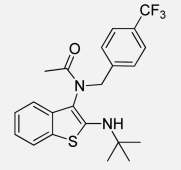
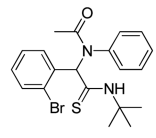
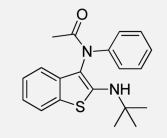
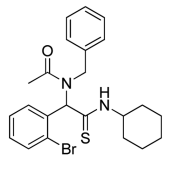
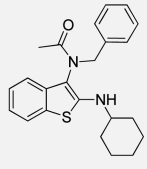
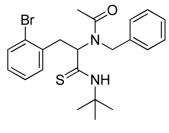
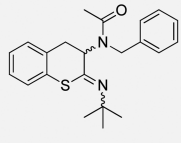
Table 3. continued

No	Ugi adducts[a,b]	Products[b,c]	No	Ugi adducts[a,b]	Products[b,c]	No	Ugi adducts[a,b]	Products[b,c]
22	 **5**{*1,2,1,2*}, **5v** 35%	80%  **8**{*1,2,1,2*}, **8v** 71%	23	43%  **5**{*1,2,1,3*}, **5w** 67%	74%  **8**{*1,2,1,3*}, **8w** 96%	24	61%  **5**{*1,2,1,4*}, **5x** 47%	76%  **8**{*1,2,1,4*}, **8x** 63%
25	 **5**{*1,2,1,6*}, **5y** 43%	 **8**{*1,2,1,6*}, **8y** 65%	26	 **5**{*1,2,1,7*}, **5z** 55%	 **8**{*1,2,1,7*}, **8z** 77%	27	 **5**{*1,2,1,8*}, **5aa** 40%	 **8**{*1,2,1,8*}, **8aa** 67%
28	 **5**{*1,1,2,1*}, **5ab** 57%	 **8**{*1,1,2,1*}, **8ab** 64%	29	 **5**{*1,1,2,4*}, **5ac** 42%	 **8**{*1,1,2,4*}, **8ac** 87%	30	 **5**{*1,1,2,8*}, **5ad** 41%	 **8**{*1,1,2,8*}, **8ad** 62%
31	 **5**{*1,2,2,1*}, **5ae** 70%	 **8**{*1,2,2,1*}, **8ae** 87%	32	 **5**{*12,1,2,1*}, **5ag** 49%	 **9**{12,1,2,1}, **9a** 52%[d]			

[a]Reaction conditions: **1**{*1*} (3 mmol), **2**{*2*} (1 equiv), **3**{*1*} (1 equiv), **4**{*1*} (1 equiv), and solvent (6 mL) at 25 °C. [b]Isolated yield. [c]Reaction conditions: **5** (0.4 mmol), Cs_2CO_3 (2 equiv), CuI (20 mol %), 1,10-phenanthroline (20 mol %) and solvent (THF/water, *v*/*v* = 95:5) under microwave irradiation at 100 °C. [d]Cs_2CO_3 (4 equiv), CuI (40 mol %), 1,10-phenanthroline (40 mol %).

purity of **8af** could be determined by HPLC using a chiral column (Scheme 2), verifying that a little racemization had occurred. Thiochroman **9a** was also produced but we failed to eliminate the byproduct suspected to be 2*H*-thiochromene, which would be derived from oxidation of the product.

Next, we turned our attention to the construction of thiazines **10** and thiazepine **11** (Table 4). The yields of thio-Ugi adducts for condensed thiazine **10** was inferior compared to the thio-Ugi for **8** and **9** because *o*-bromoaniline creates a more sterically hindered circumstance. Also, we were unable to synthesize **5bd** and **5be** which use an aldehyde with an EWG group, revealing that the electronic nature of the imine should be adjusted for the successful formation of Ugi adducts. Unfortunately, due to the failure of imine formation between **1**{*11*} and **4**{*17*}, we were also unable to synthesize **5bm**. Under identical conditions to those used for the fused benzo[*b*]thiophenes **8**, the starting materials for the synthesis of thiazine remained except for **5ba**. The problem was simply solved by increasing the amount of CuI and the ligand. When R^1(**10d**, **10g**, **10h**, **10j**, **10k**) consisted of alkyl groups that were less bulky than aromatics, the corresponding products existed as a mixture of *E* and *Z* stereoisomers whereas the other products contained only the *Z*-isomer (**10a**, **10c**, **10e**, **10f**, **10i**, **10l**).

For the synthesis of thiazepines **11**, adding more catalyst and ligand was ineffective in improving yields, although the starting materials were consumed. Attempts to develop better conditions ended in failure. Additionally, the reaction did not proceed with **5bp** possessing a benzoyl moiety. Eventually, we applied the conditions used for the benzo[*b*]thiophenes **8**. **5bq** and **5br**, respectively, gave an enamine tautomer **11a** and imine form **11b** confirmed by NMR (Table 4, entries 17 and 18). The difference in the number of sp^3-hybridized carbons between **11a** (or **11b**) and their corresponding tautomer, and coupling patterns of ^{1}H NMR in **11b** permitted the determination of the structure. Finally, the attempts to produce 8-membered rings were disappointing (Table 4, entry 19).

Only two commercial isocyanides were used for producing the heterocycles. Instead of introducing a variety of isocyanides in the first step for Ugi adducts, deprotection of *tert*-butyl group of the benzo[*b*]thiophene **8b** was carried out with trifluoroacetic acid (TFA) to make the primary arylamine that could be further diversified with electrophiles (Scheme 3). However, the obtained product was the amide **12** which we had not expected.[13] Hydrolysis of the amide **12** under the basic conditions gave the desired product **14**. In the literature, we found another condition

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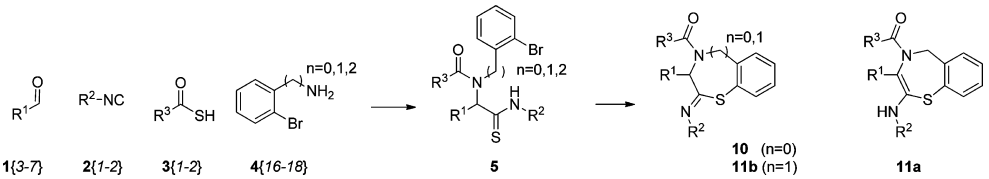
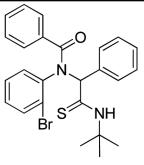
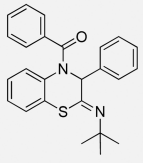
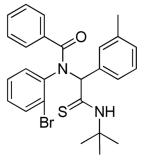
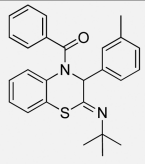
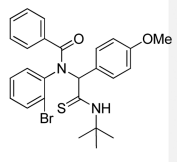
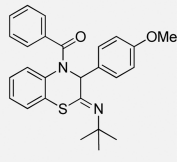
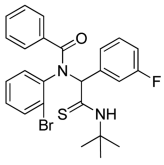
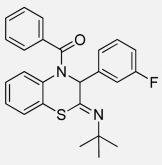
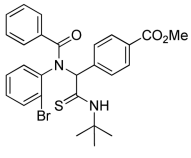
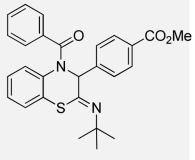
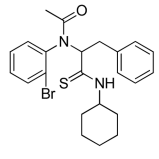
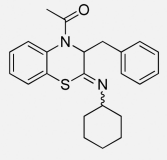
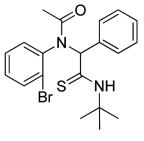
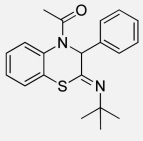
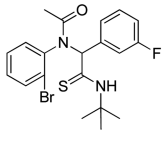
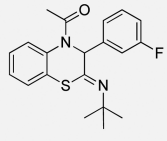
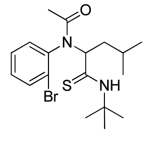
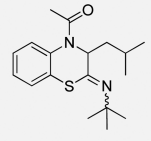
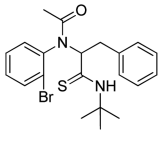
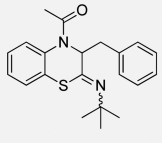
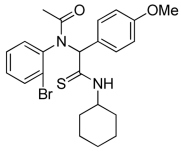
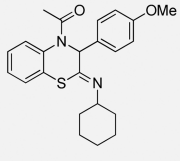
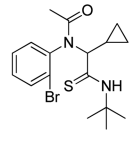
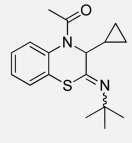
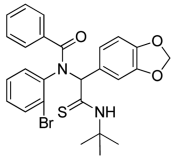
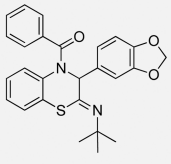
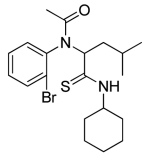
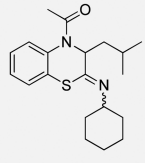
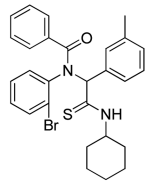
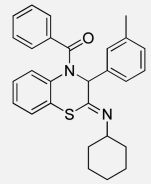
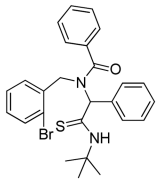
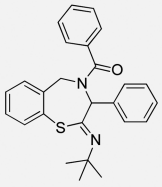
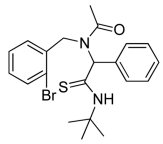
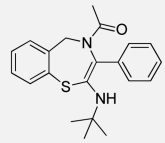
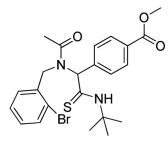
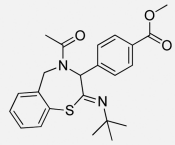
Table 4. Synthesis of Thio-Ugi Adducts and Their Corresponding Heterocycles



No	Ugi adducts[a,b]	Products[b,c]	No	Ugi adducts[a,b]	Products[b,c]	No	Ugi adducts[a,b]	Products[b,c]
1	 **5**{*3,1,1,17*}, **5ba** 17%	 **10**{*3,1,1,17*}, **10a** 64%	2	 **5**{*4,1,1,17*}, **5bb** 20%	 **10**{*4,1,1,17*}, **10b** 53%[g]	3	 **5**{*5,1,1,17*}, **5bc** 26%	 **10**{*5,1,1,17*}, **10c** 64%[d]
4	 **5**{*6,1,1,17*}, **5bd** -	 -	5	 **5**{*7,1,1,17*}, **5be** -	 -	6	 **5**{*9,2,2,17*}, **5bf** 13%	 **10**{9,2,2,17}, **10d** **57%**[d] (*E*/*Z* ratio = 24:76)[e]
7	 **5**{*3,1,2,17*}, **5bg** 29%	 **10**{*3,1,2,17*}, **10e** 68%[d]	8	 **5**{*6,1,2,17*}, **5bh** 15%	 **10**{*6,1,2,17*}, **10f** 83%[d]	9	 **5**{*8,1,2,17*}, **5bi** 24%	 **10**{8,1,2,17}, **10g** **64%**[d] (*E*/*Z* ratio = 16:84)[e]
10	 **5**{*9,1,2,17*}, **5bj** 17%	 **10**{*9,1,2,17*}, **10h** 40%[d,h] (*E*/*Z* ratio = 23:77)[e]	11	 **5**{*5,2,2,17*}, **5bk** 23%	 **10**{*5,2,2,17*}, **10i** 80%[d]	12	 **5**{*10,1,2,17*}, **5bl** 20%	 **10**{*10,1,2,17*}, **10j** 23%[d] (*E*/*Z* ratio = 17:83)[e]
13	 **5**{*11,1,1,17*}, **5bm** -	 -	14	 **5**{*8,2,2,17*}, **5bn** 26%	 **10**{*8,2,2,17*}, **10k** 57%[d] (*E*/*Z* ratio = 16:84)[e]	15	 **5**{*4,2,1,17*}, **5bo** 14%	 **10**{*4,2,1,17*}, **10l** 63%[d]
16	 **5**{*3,1,1,18*}, **5bp** 32%	 -	17	 **5**{*3,1,2,18*}, **5bq** 54%	 **11**{*3,1,2,18*}, **11a** 28%[i]	18	 **5**{*7,1,2,18*}, **5br** 49%	 **11**{*7,1,2,18*}, **11b** 9%[k]

DOI: 10.1021/acscombsci.5b00034
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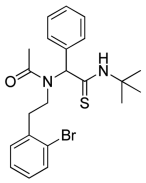
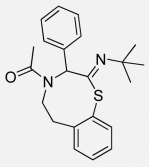
Table 4. continued

No	Ugi adducts[a,b]	Products[b,c]	No	Ugi adducts[a,b]	Products[b,c]	No	Ugi adducts[a,b]	Products[b,c]
19	 **5**{*3,1,2,19*}, **5bs** 62%	 -						

[a]Reaction conditions: **1**{*1*} (3 mmol), **2**{*2*} (1 equiv), **3**{*1*} (1 equiv), **4**{*1*} (1 equiv), and solvent (6 mL) at 25 °C. [b]Isolated yield. [c]Reaction conditions: **5** (0.4 mmol), Cs_2CO_3 (2 equiv), CuI (20 mol %), 1,10-phenanthroline (20 mol %), and solvent (THF/water, *v*/*v* = 95:5) under microwave irradiation at 100 °C. [d]Reaction conditions: **5** (0.4 mmol), Cs_2CO_3 (4 equiv), CuI (40 mol %), 1,10-phenanthroline (40 mol %), and solvent (THF/water, *v*/*v* = 95:5) under microwave irradiation at 100 °C. [e]Ratio determined by ^{1}H NMR analysis. [g]15% Ugi adducts recovered. [h]42% Ugi adducts recovered. [i]53% Ugi adducts recovered. [j]28% Ugi adducts recovered. [k]20% Ugi adducts recovered.

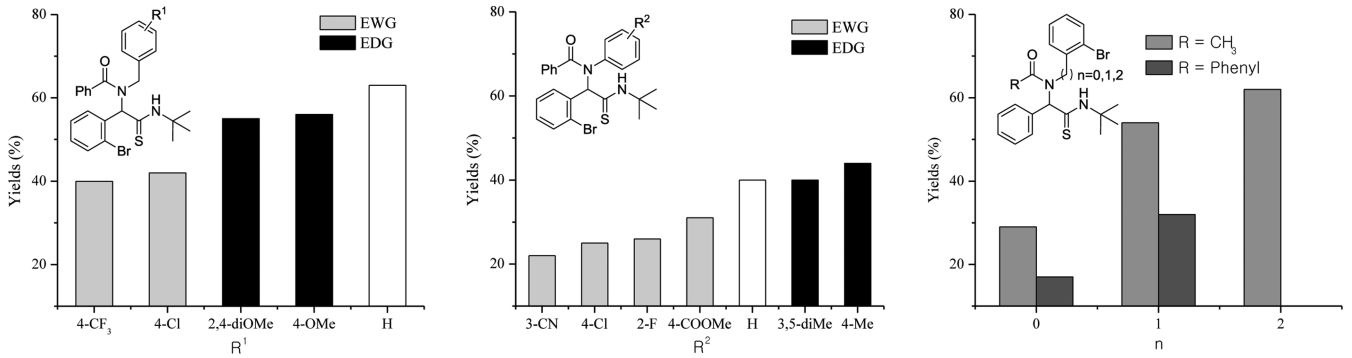
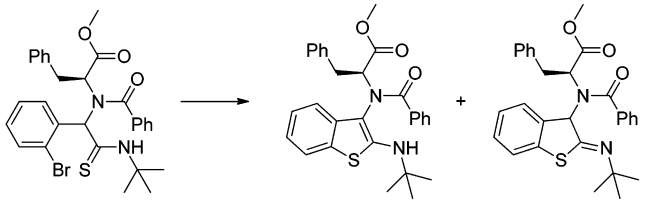


Figure 3. Comparisons of thio-Ugi Adducts' yields.

Scheme 2. Application of an Optically Pure Amino Ester[a]



5{1,1,1,16}, **5af**, 33% **8af** (61%), 97% ee **8ag** (29%), 97% ee

[a]Reaction conditions: **5** (0.4 mmol), Cs_2CO_3 (2 equiv), CuI (20 mol %), 1,10-phenanthroline (20 mol %), and solvent (THF/water, *v*/*v* = 95:5) under microwave irradiation at 100 °C.

for N-de-*tert*-butylation using BF_3 complex but it also gave the corresponding amide **13**.[2g]

CONCLUSION

In summary, we have described the synthesis of fused heterocycles by intramolecularly creating a C−S bond between thioamides generated from an Ugi reaction and aryl halides.

Furthermore, in the preparation of thio-Ugi adducts, electronic and steric effects on the reaction efficiency were briefly discussed. Biologically important derivatives of benzo[*b*]thiophenes, benzo[*b*][1,4]thiazines and thiochroman were successfully synthesized in two synthetic steps in good to excellent yields but 1,4-benzothiazepines were obtained in low yields. Although we employed inexpensive copper(I) iodide and a ligand for the C−S bond formation, it is necessary to seek better catalysts and ligands because constructing rings larger than five-membered rings requires high loading of catalysts and ligands.

EXPERIMENTAL PROCEDURES

General Procedure for Preparation of Thio-Ugi Adducts 5. The aldehyde **1**{*1*} (3 mmol) was added to the amine **4**{*1*} (1 equiv). The reaction mixture was stirred at room temperature for the imine formation for 1−2 h. Then, TFE (6 mL), the isocyanide **2**{*1*} (1 equiv) and the thio acid **3**{*1*} (1 equiv) was added slowly to the reaction mixture and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the residue was purified by column chromatography on silica gel with an ethyl acetate/hexanes mixture as eluents to give thio-Ugi adducts **5**{*1,1,1,1*}, **5a** (63%): White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.62−7.52 (m, 3H), 7.47−7.37 (m, 4H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.20−7.14 (m, 3H), 7.12−7.04 (m, 3H), 5.86 (s, 1H), 5.20−4.54 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.09, 173.62, 136.96, 135.91, 135.86, 133.05, 131.45, 130.23, 129.93, 128.49, 128.45, 128.44, 127.61, 127.50, 127.36, 125.50, 76.67, 56.94, 55.81, 27.16; LC/MS (ESI) *m*/*z* 495 $[M + H]^+$.

General Procedure for Preparation of Benzo[*b*]-thiophene 8 and S-Heterocycles 9−11. K_3PO_4 (2 quiv), CuI (20 mol %), and 1,10-phenanthroline (20 mol %) was added to a stirred solution of Ugi adduct **5**{*1,1,1,2*} (0.40 mmol) in 4.75 mL of THF and 0.25 mL of H_2O (THF/H_2O = 95:5, *v*:*v*). The reaction mixture was subjected to microwave heating (100 °C) for 1 h and then the reaction mixture were concentrated under reduced pressure. Water was added to the

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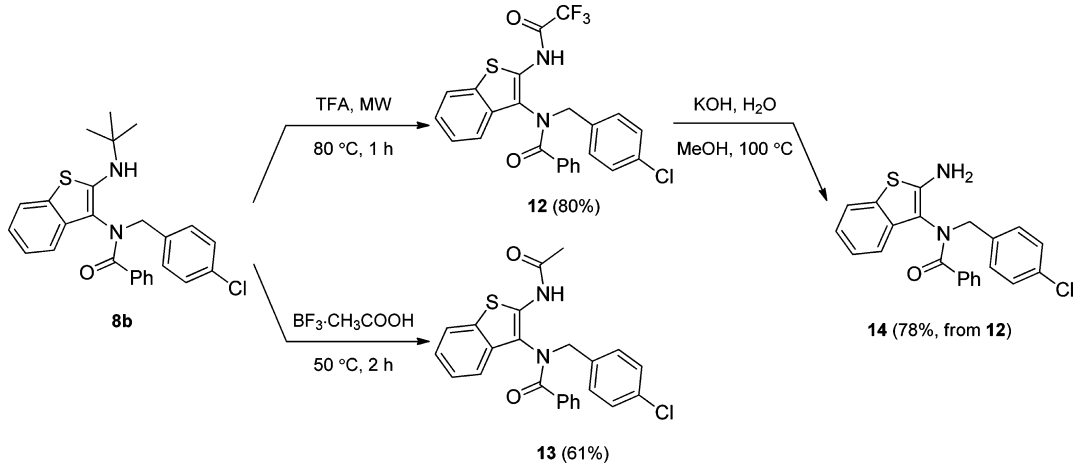
Scheme 3. N-De-*tert*-butylation of 8b



crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the residue was purified by column chromatography using ethyl acetate and hexanes as eluents to give the desired products **8**{*1,1,1,2*}, **8b** (94%): Pale yellow solid; mp 140−141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 7.9 Hz, 1H), 7.35−7.29 (m, 6H), 7.25 (d, J = 8.2 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 7.10 (ddd, J = 8.1, 5.1, 3.3 Hz, 1H), 7.05 (t, J = 7.7 Hz, 2H), 5.68 (d, J = 13.5 Hz, 1H), 4.17 (d, J = 13.5 Hz, 1H), 3.40 (s, 1H), 0.92 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.30, 146.59, 136.75, 135.52, 135.32, 133.91, 131.20, 130.11, 129.21, 128.73, 127.35, 126.91, 125.10, 121.95, 121.27, 117.07, 110.96, 51.92, 50.19, 28.89; HRMS (ESI) m/z calcd for $C_{26}H_{26}ClN_2OS$ $[M + H]^+$ 449.1449, found 449.1449.

(Z)-(2-(tert-Butylimino)-3-phenyl-2H-benzo[b][1,4]thiazin-4(3H)-yl)(phenyl)methanone ***10a:*** Isolated yield, 64%; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.7 Hz, 2H), 7.35 (t, J = 7.4 Hz, 1H), 7.26 (t, J = 7.0 Hz, 4H), 7.20−7.13 (m, 3H), 7.10 (t, J = 7.2 Hz, 1H), 6.90 (t, J = 7.6 Hz, 2H), 6.71 (t, J = 6.5 Hz, 1H), 6.51 (s, 1H), 1.52 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.97, 152.27, 136.80, 136.61, 134.81, 130.82, 129.13, 128.44, 128.19, 128.10, 127.45, 127.03, 126.90, 126.85, 126.02, 125.77, 62.15, 57.21, 28.98; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2OS$ $[M + H]^+$ 401.1682, found 401.1683.

1-(2-(tert-Butylamino)-3-phenylbenzo[f][1,4]thiazepin-4(5H)-yl)ethan-1-one ***11a:*** Isolated yield, 28%; pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.5 Hz, 2H), 7.37 (dd, J = 15.3, 7.5 Hz, 3H), 7.26−7.18 (m, 2H), 7.17−7.09 (m, 2H), 5.84−5.54 (m, 1H), 4.12 (s, 1H), 4.07−3.85 (m, 1H), 2.19 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.67, 146.70, 136.13, 135.52, 131.21, 129.28, 129.19, 129.03, 127.49, 126.83, 126.56, 126.11, 122.48, 53.83, 46.91, 31.31, 21.48; HRMS (ESI) m/z calcd for $C_{21}H_{25}N_2OS$ $[M + H]^+$ 353.1682, found 353.1682.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ^{1}H NMR and ^{13}C NMR data and spectra for products **5**−**14**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00034.

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Notes

The authors declare no competing financial interest.

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