JOC The Journal of Organic Chemistry

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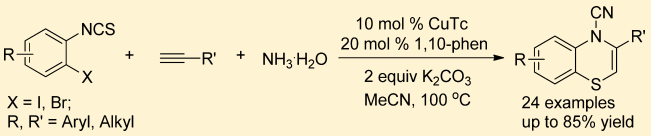
Copper-Catalyzed Three-Component Tandem Cyclization for One-Pot Synthesis of 1,4-Benzothiazines

Jing-Jing Chu, Bo-Lun Hu, Zhi-Yong Liao, and Xing-Guo Zhang*

College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, China

Supporting Information

ABSTRACT: A copper-catalyzed three-component tandem reaction has been developed for the convenient and practical synthesis of 1,4-benzothiazines. A variety of terminal alkynes and 2-iodo/bromophenyl isothiocyanates underwent this one-pot cyclization with aqueous ammonia to afford 1,4-benzothiazines in moderate to good yields.



1,4-Benzothiazine derivatives are important heterocyclics and widely exist in a great number of natural products and biologically active molecules, which possess a broad spectrum of biological activities, such as antibacterial,[1] antidiabetic,[2] antiarrhythmic,[3] and antitumor.[4] Therefore, sustainably increasing attention has been directed toward their synthesis in synthetic and medicinal chemistry areas.[5]

In the past decades, transition-metal-catalyzed coupling reaction of aryl halides with thiol surrogates has been developed for the synthesis of organosulfur compounds.[6] For example, Paradies and co-workers reported the Pd-catalyzed tandem reaction of aryl halides and thiourea for the synthesis of thioethers and benzothiophenes.[7] Aryl thioureas are also versatile sufuration reagents,[8] and could be prepared from the addition of aryl isothiocyanates and aqueous ammonia, which is one of the most abundant and low cost nitrogen sources for the production of fertilizers and nitrogen-containing molecules.[9] Meanwhile, one-pot multistep tandem reaction has emerged as a powerful tool in the synthesis of complex organic molecules, owing to their advantage in improving atom economy, saving time, and efficient formation of multiple bonds without separation.[10] Therefore, the development of multifunctional catalytic system which is compatible for several mechanistically diverse reactions in tandem reactions is still highly desirable. Herein, we wish to report a copper-catalyzed three-component tandem reaction of *o*-halophenyl isothiocyanates, terminal alkynes and aqueous ammonia for one-pot synthesis of 1,4-benzothiazines. The reaction pathway involves desulfhydrylation of aryl thioureas, a double C−S bond forming reaction, and intramolecular hydroamination (Scheme 1).

We began our study by exploring the reaction of 1-iodo-2-isothiocyanatobenzene **1a**[11] with ethynylbenzene **2a** and aqueous ammonia to screen the reaction conditions, and the results are summarized in Table 1. First, a variety of copper catalysts were examined (entries 1−6), and moderate yields were obtained in the presence of cupric or cuprous salts

Scheme 1. Tandem Cyclization for the Synthesis of 1,4-Benzothiazines

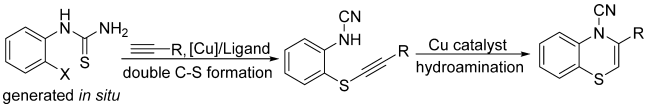
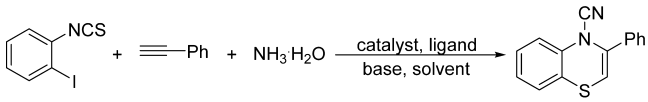


Table 1. Screening Conditions



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

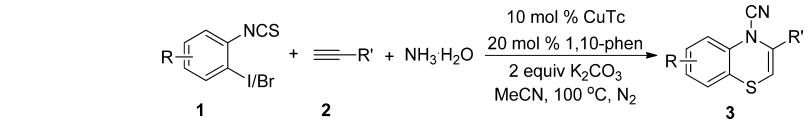
entry	catalyst	ligand	base	solvent	yield
1	CuCl		K_2CO_3	CH_3CN	52%
2	CuBr		K_2CO_3	CH_3CN	62%
3	CuI		K_2CO_3	CH_3CN	66%
4	$Cu(OAc)_2$		K_2CO_3	CH_3CN	61%
5	$Cu(OTf)_2$		K_2CO_3	CH_3CN	62%
6	CuTc		K_2CO_3	CH_3CN	69%
7			K_2CO_3	CH_3CN	0
8	CuTc	TMEDA	K_2CO_3	CH_3CN	68%
9	CuTc	L-proline	K_2CO_3	CH_3CN	66%
10	CuTc	bipyridine	K_2CO_3	CH_3CN	74%
11	CuTc	1,10-phen	K_2CO_3	CH_3CN	85%
12	CuTc	1,10-phen	K_3PO_4	CH_3CN	73%
13	CuTc	1,10-phen	Cs_2CO_3	CH_3CN	70%
14	CuTc	1,10-phen	NEt_3	CH_3CN	24%
15	CuTc	1,10-phen	K_2CO_3	DMF	75%
16	CuTc	1,10-phen	K_2CO_3	DMSO	64%
17	CuTc	1,10-phen	K_2CO_3	THF	43%
18	CuTc	1,10-phen	K_2CO_3	H_2O	11%
19[b]	CuTc	1,10-phen	K_2CO_3	CH_3CN	57%
20[c]	CuTc	1,10-phen	K_2CO_3	CH_3CN	76%

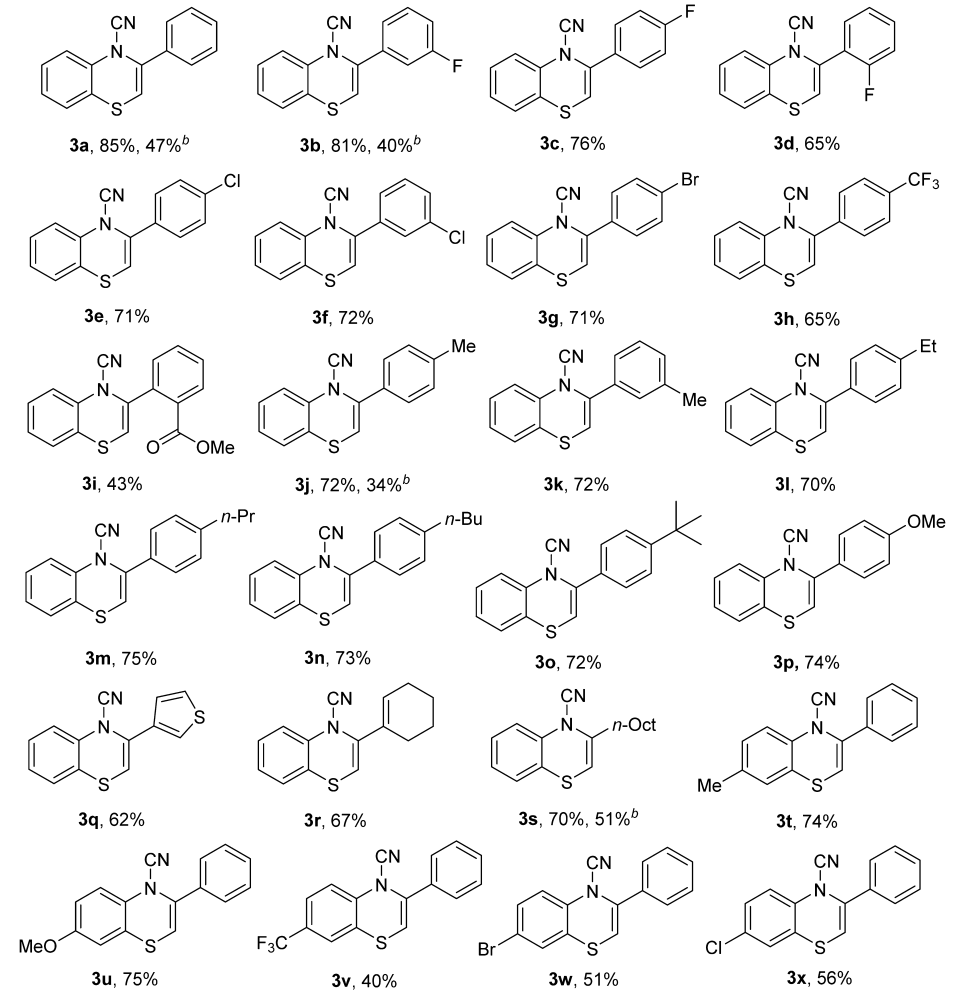
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), aqueous ammonia (1.0 mmol), copper salts (10 mol%), ligand (20 mol%), and base (2 equiv) in solvent (2 mL) under N_2 at 100 °C for 12 h. [b]At 80 °C. [c]Under air.

Received: July 12, 2016
Published: August 25, 2016

DOI: 10.1021/acs.joc.6b01668
J. Org. Chem. 2016, 81, 8647−8652

Table 2. Scope of the Reaction





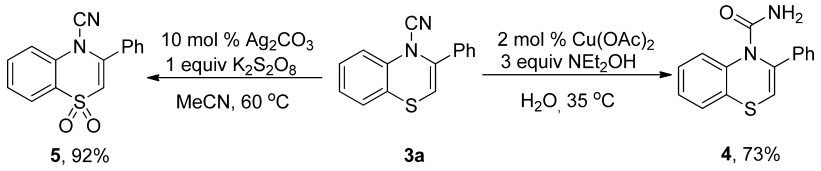
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), aqueous ammonia (1.0 mmol), CuTc (10 mol%), 1,10-phenanthroline (20 mol%), and K_2CO_3 (0.4 mmol) in MeCN (2 mL) under N_2 for 12 h, isolated yield. [b]*o*-Bromophenyl isothiocyanate and 20 mol% CuTc were used.

including CuCl, CuBr, CuI, $Cu(OAc)_2$, $Cu(OTf)_2$, and copper(I) thiophene-2-carboxylate (CuTc). Treatment of substrate **1a** with **2a**, aqueous ammonia, 10 mol% CuTc, and 2 equiv of K_2CO_3 in MeCN afforded the desired product **3a** in 69% yield (entry 6). The reaction did not work in the absence of copper catalysts (entry 7). In order to improve the reaction yields, we investigated some nitrogen ligands, such as tetramethyldiaminoethane (TMEDA), L-proline, bipyridine, and 1,10-phenanthroline (1,10-phen) (entries 8−11). The results disclosed that 1,10-phenanthroline was the most effective ligand to give the product **3a** in 85% yield (entry 11). Subsequently, various bases were tested with aim of promoting C−S bond formation of aryl iodides (entries 12−14). However, lower yields were obtained for K_3PO_4 and Cs_2CO_3, and only 24% yield was observed when NEt_3 was used as base (entry 14). During the screening of solvents, DMF, DMSO, THF, and H_2O were found to be inferior to MeCN (entries 15−18). The yield was decreased to 57% when the reaction was carried out at 80 °C (entry 19), and 76% yield was obtained when the reaction was performed under air atmosphere (entry 20).

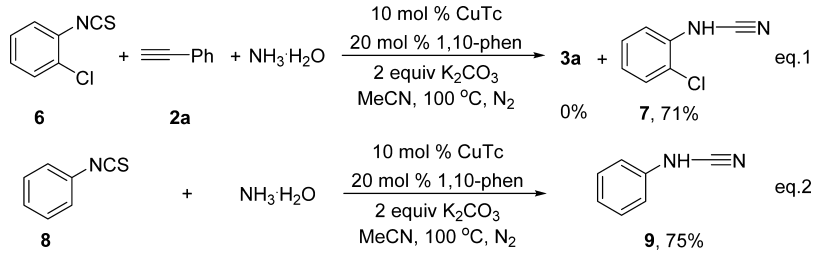
Under the optimal reaction conditions, we explored the scope of this three-component cyclization by examining a variety of terminal alkynes and isothiocyanates. As shown in Table 2, both electron-withdrawing and electron-donating groups were compatible for alkyne or isothiocyanate moiety, and the corresponding products were obtained in moderate to good yields. It is noteworthy that *o*-bromophenyl isothiocyanate was also suitable substrate to produce **3a** in 47% yield by treatment with alkyne **2a** in the presence of 20 mol% CuTc. Similarly, a 40% yield was obtained when *o*-bromophenyl isothiocyanate was reacted with 3-fluorophenylethyne. Nevertheless, *o*-iodophenyl isothiocyanates provided better results owing to the reactive C−I bond in coupling reaction. For example, the reactions of substrate **2a** with fluoride phenylethyne afforded products **3b**−**3d** in 65−81% yields. Chloride and bromide products **3e**−**3g** were isolated in 71−72% yields. Electron-poor trifluoromethyl phenylethyne gave product **3h** in 65% yield, and bulky methyl-2-ethynylbenzoate afforded

DOI: 10.1021/acs.joc.6b01668
J. Org. Chem. 2016, 81, 8647−8652

Scheme 2. Synthetic Applications of 3a



Scheme 3. Control Experiment



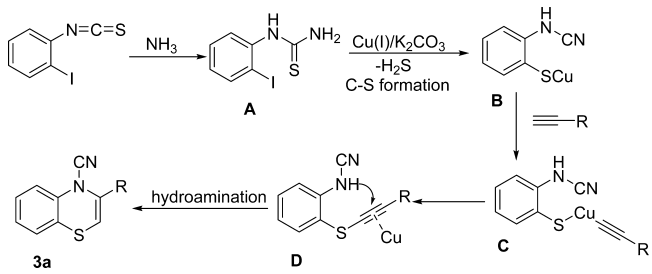
product **3i** in 43% yield. As expected, phenylethynes bearing Me, Et, *n*-Pr, *n*-Bu, *t*-Bu, and OMe groups underwent the cyclization smoothly to afford the corresponding products **3j**−**3p** in 70−75% yields. Heteroaromatic 3-ethynylthiophene also produced the corresponding product **3q** in 62% yield. Interestingly, the reactions of aliphatic alkynes were performed successfully under standard conditions. For instance, 1-ethynylcyclohex-1-ene and dec-1-yne furnished product **3r** and **3s** in 67% and 70% yields, respectively. A 51% yield was also observed when dec-1-yne was conducted with *o*-bromophenyl isothiocyanate and aqueous ammonia. Subsequently, substituents on *o*-iodophenyl isothiocyanate moiety were tested under the optimized reaction conditions. Electron-donating methyl and methoxy afforded product **3t** and **3u** in 74% and 75% yields, while electron-withdrawing trifluoromethyl gave product **3v** in 40% yields. *o*-Iodophenyl isothiocyanate with a bromo or chloro group could also be transformed to benzothiazine **3w** and **3x** in 51% and 56% yields, respectively.

To demonstrate the applicability of this reaction in the synthesis of diversely functionalized 1,4-benzothiazines, further transformation of product **3a** was explored as outlined in Scheme 2. The hydration of cyano group was realized by treatment of **3a** with 2 mol% $Cu(OAc)_2$ and 3 equiv NEt_2OH in water, 1,4-benzothiazine-4-carboxamide **4** was isolated in 73% yield.[12] Furthermore, in the presence of 10 mol% Ag_2CO_3 and 1 equiv $K_2S_2O_8$, product **3a** was oxidized to benzo[b]-[1,4]thiazine 1,1-dioxide **5** in 92% yield, which has been reported to possess strong antimicrobial activity.[13]

In order to probe the mechanism and extend substrate scope of this one-pot cyclization, the reaction of *o*-chlorophenyl isothiocyanate **6** with phenylethyne **2a** and aqueous ammonia was conducted under standard conditions (Scheme 3, eq 1). To our surprise, both the desired product **3a** and addition product 2-chlorophenyl thioureas could not be observed, while *N*-(2-chlorophenyl)cyanamide **7** was isolated in 71% yield. These results suggested that elimination of 2-chlorophenyl thioureas occurred to generate cyanamide **7** and hydrogen sulfide, but the cross-coupling reaction did not proceed due to the less reactivity of aryl chloride. To further confirm the desulfhydrylation of aryl thioureas, phenyl isothiocyanate **8** was treated with aqueous ammonia under standard conditions. As expected, *N*-phenylcyanamide **9** was obtained in 75% yield (eq 2).

On the basis of the obtained results and previous reports,[14] a plausible mechanistic pathway is outlined in Scheme 4. First,

Scheme 4. Possible Mechanism



the addition of aqueous ammonia to *o*-iodophenyl isothiocyanate yields 2-iodophenyl thioureas **A**. The desulfhydrylation of thioureas **A** and following C−S formation in the presence of CuTc and K_2CO_3 occurs to produce cyanamide **B**, which undergoes another cross-coupling reaction with alkyne to afford intermediate **C**. Then, reductive elimination of intermediate **C** generates alkynyl thioether **D**, the final copper-catalyzed intramolecular hydroamination gives the cyclization product **3a**. However, the ring opening of 2-aminobenzothiazoles pathway cannot be ruled out.[5a]

In summary, we have developed a copper-catalyzed three-component tandem reaction for the convenient and practical synthesis of 1,4-benzothiazines from readily accessible starting materials. The elimination of aryl thioureas generated *in situ* afforded dihydrosulfide surrogate, which triggered the following double C−S formation and intramolecular hydroamination. A variety of terminal alkynes and 2-iodo/bromophenyl isothiocyanates underwent this tandem cyclization with aqueous ammonia to give 1,4-benzothiazines in moderate to good yields. Moreover, the synthetic utility of this method was investigated by the oxidation and hydration of the obtained product, and its derivative carboxamide and sulfone could be prepared easily in good yields. The present process provided a valuable new approach for the construction of 1,4-benzothiazine scaffold, which will be useful in the synthesis of heterocyclics.

EXPERIMENTAL SECTION

General Information. Chemicals were either purchased or purified by standard techniques. ^1H NMR and ^{13}C NMR spectra

DOI: 10.1021/acs.joc.6b01668
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were measured on a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. High-resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometer. All reactions under nitrogen atmosphere were conducted using standard Schlenk techniques. Melting point data are uncorrected. Column chromatography was performed using EM silica gel 60 (300−400 mesh).

General Process for the Synthesis of 1,4-Benzothiazine. 2-Iodophenyl isothiocyanate **1a** (0.2 mmol, 52.2 mg), phenylacetylene **2a** (0.3 mmol, 30.6 mg), aqueous ammonia (1.0 mmol, 125 mg, wt% = 28−30%), copper(I) thiophene-2-carboxylate (CuTc; 10 mol %, 3.8 mg), K_2CO_3 (0.4 mmol, 55.2 mg), and 1,10-phenanthroline (20 mol %, 7.2 mg) in the CH_3CN (2.0 mL) were added in Schlenk at 100 °C under N_2. The solution was stirred for 12 h. Then after the removal of solvent, the product was purified by column chromatography (petroleum ether (PE)/ethyl acetate (EA), v/v = 10:1).

3-Phenyl-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3a**).[5b] Yellow solid (42.3 mg, 85%); mp 127−128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.42 (m, 5H), 7.38−7.36 (m, 1H), 7.29−7.26 (m, 1H), 7.17−7.14 (m, 1H), 7.11−7.09 (m, 1H), 5.76 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 136.2, 132.3, 129.8, 128.9, 128.1, 127.2, 127.12, 127.10, 125.4, 118.5, 110.4, 106.2; LRMS (EI, 70 eV) m/z (%): 250 (M^+, 100), 223 (20), 218 (11), 121 (9).

3-(3-Fluorophenyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3b**). Yellow solid (43.3 mg, 81%); mp 81−82 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.31 (m, 1H), 7.29−7.27 (m, 1H), 7.22−7.19 (m, 1H), 7.15−7.13 (m, 1H), 7.10−7.07 (m, 1H), 7.06−7.01 (m, 3H), 5.76 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8 (d, J_{C-F} = 246.5 Hz), 136.0, 134.42, 134.35, 130.6, 128.2, 127.2 (d, J_{C-F} = 20.1 Hz), 125.2, 122.8, 118.7, 116.8 (d, J_{C-F} = 21.1 Hz), 114.3, 114.2, 110.2, 108.0; LRMS (EI, 70 eV) m/z (%): 268 (M^+, 100), 241 (22), 236 (16); HRMS (ESI): Calcd for $C_{15}H_{10}FN_2S^+$ ([M+H]$^+$): 269.0543, Found: 269.0556.

3-(4-Fluorophenyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3c**). Yellow solid (40.7 mg, 76%); mp 118−119 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.32 (m, 2H), 7.28−7.26 (m, 1H), 7.21−7.17 (m, 1H), 7.10−7.06 (m, 1H), 7.05−7.00 (m, 3H), 5.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5 (d, J_{C-F} = 249.3 Hz), 136.5, 136.0, 129.2, 128.5, 128.1, 127.2, 127.1, 125.2, 118.5, 116.1 (d, J_{C-F} = 21.9 Hz), 110.2, 106.2; LRMS (EI, 70 eV) m/z (%): 268 (M^+, 100), 241 (21), 236 (16); HRMS (ESI): Calcd for $C_{15}H_{10}FN_2S^+$ ([M+H]$^+$): 269.0543, Found: 269.0559.

3-(2-Fluorophenyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3d**). Yellow solid (34.7 mg, 65%); mp 107−108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.29 (m, 2H), 7.26−7.25 (m, 1H), 7.22−7.18 (m, 1H), 7.15−7.12 (m, 1H), 7.10−7.06 (m, 2H), 7.04−7.02 (m, 1H), 5.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (d, J_{C-F} = 249.8 Hz), 136.1, 132.3, 131.9, 131.8, 130.7, 128.2, 127.14, 127.08, 124.7, 120.4, 118.2, 116.4 (d, J_{C-F} = 21.3 Hz), 109.9, 109.2; LRMS (EI, 70 eV) m/z (%): 268 (M^+, 100), 241 (16), 121 (15); HRMS (ESI): Calcd for $C_{15}H_{10}FN_2S^+$ ([M+H]$^+$): 269.0543, Found: 269.0558.

3-(4-Chlorophenyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3e**). Yellow solid (40.3 mg, 71%); mp 123−124 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.30 (m, 2H), 7.29−7.26 (m, 3H), 7.21−7.18 (m, 1H), 7.10−7.07 (m, 1H), 7.02−7.00 (m, 1H), 5.69 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 136.0, 135.8, 130.8, 129.2, 128.4, 128.2, 127.3, 127.1, 125.1, 118.6, 110.2, 107.1; LRMS (EI, 70 eV) m/z (%): 284 (M^+, 100), 286 (39), 249 (33), 222 (31); HRMS (ESI): Calcd for $C_{15}H_{10}ClN_2S^+$ ([M+H]$^+$): 285.0248, Found: 285.0249.

3-(3-Chlorophenyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3f**). Yellow solid (41.1 mg, 72%); mp 114−115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.30−7.27 (m, 3H), 7.25−7.22 (m, 1H), 7.21−7.18 (m, 1H), 7.11−7.08 (m, 1H), 7.03−7.01 (m, 1H), 5.75 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 135.9, 135.0, 134.1, 130.2, 129.9, 128.3, 127.4, 127.3, 127.2, 125.2, 125.1, 118.7, 110.1, 108.0; LRMS (EI, 70 eV) m/z (%): 284 (M^+, 100), 286 (36), 249 (39); HRMS (ESI): Calcd for $C_{15}H_{10}ClN_2S^+$ ([M+H]$^+$): 285.0248, Found: 285.0254.

3-(4-Bromophenyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3g**). Yellow solid (46.9 mg, 71%); mp 131−132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56−7.54 (m, 2H), 7.36−7.34 (m, 1H), 7.30−7.26 (m, 3H), 7.18−7.15 (m, 1H), 7.10−7.08 (m, 1H), 5.78 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 135.9, 132.1, 131.2, 128.6, 128.2, 127.3, 127.1, 125.1, 124.1, 118.6, 110.2, 107.2; LRMS (EI, 70 eV) m/z (%): 328/330 (M^+, 100), 249 (51), 222 (56), 124 (18); HRMS (ESI): Calcd for $C_{15}H_{10}BrN_2S^+$ ([M+H]$^+$): 328.9743, Found: 328.9750.

3-(4-(Trifluoromethyl)phenyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3h**). Yellow solid (41.2 mg, 65%); mp 108−109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62−7.61 (m, 2H), 7.49−7.47 (m, 2H), 7.31−7.29 (m, 1H), 7.24−7.21 (m, 1H), 7.13−7.10 (m, 1H), 7.05−7.03 (m, 1H), 5.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 135.82, 135.81, 135.78, 131.6 (q, J_{C-F} = 32.6 Hz), 128.4, 127.4, 127.2, 126.0, 124.9, 123.7 (q, J_{C-F} = 270.8 Hz), 118.7, 110.1, 109.1; LRMS (EI, 70 eV) m/z (%): 318 (M^+, 100), 286 (11), 249 (16), 121 (11); HRMS (ESI): Calcd for $C_{16}H_{10}F_3N_2S^+$ ([M+H]$^+$): 319.0511, Found: 319.0518.

Methyl 2-(4-Cyano-4H-benzo[b][1,4]thiazin-3-yl)benzoate (**3i**). Yellow solid (26.5 mg, 43%); mp 111−112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09−8.07 (m, 1H), 7.60−7.57 (m, 1H), 7.54−7.51 (m, 1H), 7.44−7.42 (m, 1H), 7.26−7.23 (m, 1H), 7.20−7.19 (m, 1H), 7.15−7.12 (m, 1H), 7.09−7.08 (m, 1H), 5.47 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 136.97, 136.94, 133.6, 132.70, 132.5, 131.2, 130.2, 129.9, 127.9, 127.0, 126.8, 122.9, 117.5, 109.7, 104.2, 52.4; LRMS (EI, 70 eV) m/z (%): 308 (M^+, 100), 276 (47), 248 (58), 222 (15); HRMS (ESI): Calcd for $C_{17}H_{12}N_2NaO_2S^+$ ([M+Na]$^+$): 331.0512, Found: 331.0525.

3-(p-Tolyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3j**).[5a] Yellow solid (38.1 mg, 72%); mp 95−96 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.35 (m, 1H), 7.32−7.31 (m, 2H), 7.28−7.25 (m, 1H), 7.23−7.21 (m, 2H), 7.17−7.13 (m, 1H), 7.10−7.08 (m, 1H), 5.69 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1, 137.7, 136.3, 129.6, 129.5, 128.0, 127.13, 127.10, 127.07, 125.5, 118.5, 110.5, 105.1, 21.3; LRMS (EI, 70 eV) m/z (%): 264 (M^+, 100), 249 (16), 232 (12).

3-(m-Tolyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3k**). Yellow solid (37.9 mg, 72%); mp 144−145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.28 (m, 1H), 7.23−7.12 (m, 5H), 7.08−7.05 (m, 1H), 7.01−7.00 (m, 1H), 5.64 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 137.7, 136.4, 132.4, 130.7, 128.7, 128.0, 127.9, 127.08, 127.06, 125.4, 124.3, 118.5, 110.4, 105.9, 21.3; LRMS (EI, 70 eV) m/z (%): 264 (M^+, 100), 249 (21), 231 (12); HRMS (ESI): Calcd for $C_{16}H_{13}N_2S^+$ ([M+H]$^+$): 265.0794, Found: 265.0795.

3-(4-Ethylphenyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3l**). Yellow solid (39.1 mg, 70%); mp 79−80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.33 (m, 3H), 7.28−7.24 (m, 3H), 7.16−7.13 (m, 1H), 7.10−7.08 (m, 1H), 5.70 (s, 1H), 2.67 (q, J = 7.5 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 137.7, 136.3, 129.7, 128.4, 128.0, 127.2, 127.09, 127.06, 125.5, 118.5, 110.5, 105.2, 28.6, 15.2; LRMS (EI, 70 eV) m/z (%): 278 (M^+, 100), 263 (50), 249 (19); HRMS (ESI): Calcd for $C_{17}H_{15}N_2S^+$ ([M+H]$^+$): 279.0950, Found: 279.0963.

3-(4-Propylphenyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3m**). Yellow oil (43.8 mg, 75%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.33 (m, 3H), 7.29−7.28 (m, 1H), 7.24−7.22 (m, 2H), 7.18−7.15 (m, 1H), 7.11−7.10 (m, 1H), 5.72 (s, 1H), 2.61 (t, J = 7.5 Hz, 2H), 1.68−1.62 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 137.7, 136.4, 129.7, 128.9, 128.0, 127.07, 127.06, 127.05, 125.6, 118.5, 110.5, 105.2, 37.8, 24.2, 13.8; LRMS (EI, 70 eV) m/z (%): 292 (M^+, 100), 263 (89), 236 (15); HRMS (ESI): Calcd for $C_{18}H_{17}N_2S^+$ ([M+H]$^+$): 293.1107, Found: 293.1112.

3-(4-Butylphenyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3n**). Yellow oil (44.6 mg, 73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.28 (m, 1H), 7.26−7.24 (m, 2H), 7.20−7.17 (m, 1H), 7.15−7.13 (m, 2H), 7.08−7.05 (m, 1H), 7.02−7.00 (m, 1H), 5.62 (s, 1H), 2.54 (t, J = 8.0 Hz, 2H), 1.56−1.49 (m, 2H), 1.30−1.26 (m, 2H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 137.7, 136.4, 129.6, 128.9, 128.0, 127.09, 127.08, 127.05, 125.6, 118.5, 110.5, 105.2, 35.4, 33.2, 22.3, 13.9; LRMS (EI, 70 eV) m/z (%): 306 (M^+, 100), 263 (85),

DOI: 10.1021/acs.joc.6b01668
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236 (15); HRMS (ESI): Calcd for $C_{19}H_{19}N_2S^+$ ([M+H]$^+$): 307.1263, Found: 307.1267.

*3-(4-(tert-Butyl)phenyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3o**).* Yellow solid (44.0 mg, 72%); mp 125−126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.35 (m, 2H), 7.31−7.28 (m, 3H), 7.22−7.19 (m, 1H), 7.10−7.07 (m, 1H), 7.04−7.02 (m, 1H), 5.65 (s, 1H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 137.7, 136.4, 129.4, 128.0, 127.1, 126.93, 126.92, 125.9, 125.6, 118.6, 110.6, 105.3, 34.8, 31.2; LRMS (EI, 70 eV) *m*/*z* (%): 306 (M$^+$, 100), 291 (81), 250 (30), 132 (24); HRMS (ESI): Calcd for $C_{19}H_{19}N_2S^+$ ([M+H]$^+$): 307.1263, Found: 307.1267.

*3-(4-Methoxyphenyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3p**).*[5a] Yellow solid (41.5 mg, 74%); mp 122−123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.35 (m, 3H), 7.27−7.24 (m, 1H), 7.16−7.13 (m, 1H), 7.09−7.08 (m, 1H), 6.94−6.92 (m, 2H), 5.62 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 137.6, 136.3, 128.7, 127.9, 127.1, 127.0, 125.6, 124.6, 118.5, 114.3, 110.5, 104.1, 55.3; LRMS (EI, 70 eV) *m*/*z* (%): 280 (M$^+$, 100), 265 (43), 237 (16).

*3-(Thiophen-3-yl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3q**).* Yellow solid (31.6 mg, 62%); mp 96−97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.51 (m, 1H), 7.37−7.34 (m, 2H), 7.28−7.25 (m, 1H), 7.17−7.14 (m, 2H), 7.10−7.09 (m, 1H), 5.82 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 133.2, 132.8, 128.1, 127.2, 126.8, 126.0, 125.9, 125.5, 124.4, 118.8, 110.5, 105.8; LRMS (EI, 70 eV) *m*/*z* (%): 256 (M$^+$, 100), 229 (33), 211 (16), 108 (9); HRMS (ESI): Calcd for $C_{13}H_8N_2NaS_2^+$ ([M+Na]$^+$): 279.0021, Found: 279.0034.

*3-(Cyclohex-1-en-1-yl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3r**).* Yellow oil (33.9 mg, 67%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.27 (m, 1H), 7.25−7.22 (m, 1H), 7.15−7.08 (m, 2H), 6.19 (t, *J* = 4.0 Hz, 1H), 5.67 (s, 1H), 2.23−2.20 (m, 2H), 2.18−2.15 (m, 2H), 1.75−1.70 (m, 2H), 1.65−1.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 136.6, 130.3, 129.7, 127.9, 127.0, 126.90, 126.87, 119.2, 111.3, 105.2, 26.2, 25.4, 22.2, 21.6; LRMS (EI, 70 eV) *m*/*z* (%): 254 (M$^+$, 100), 239 (19), 221 (21); HRMS (ESI): Calcd for $C_{15}H_{15}N_2S^+$ ([M+H]$^+$): 255.0950, Found: 255.0951.

*3-Octyl-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3s**).* Yellow oil (40.0 mg, 70%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14−7.10 (m, 2H), 7.02−6.99 (m, 1H), 6.95−6.94 (m, 1H), 5.20 (s, 1H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.49−1.45 (m, 2H), 1.27−1.17 (m, 10H), 0.79 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 134.5, 126.7, 126.1, 125.6, 122.7, 116.4, 108.8, 100.0, 31.8, 30.7, 28.1, 28.0, 27.7, 26.1, 21.6, 13.0; LRMS (EI, 70 eV) *m*/*z* (%): 286 (M$^+$, 100), 188 (33), 155 (25); HRMS (ESI): Calcd for $C_{17}H_{23}N_2S^+$ ([M+H]$^+$): 287.1576, Found: 287.1577.

*7-Methyl-3-phenyl-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3t**).*[5b] Yellow solid (38.9 mg, 74%); mp 119−120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.40 (m, 5H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.91 (s, 1H), 5.75 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 137.3, 133.7, 132.5, 129.8, 128.9, 128.7, 127.5, 127.2, 125.0, 118.4, 110.6, 106.1, 20.6; LRMS (EI, 70 eV) *m*/*z* (%): 264 (M$^+$, 100), 236 (13), 231 (16).

*7-Methoxy-3-phenyl-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3u**).*[5b] Yellow solid (41.9 mg, 75%); mp 126−127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.41 (m, 5H), 7.27 (d, *J* = 8.5 Hz, 1H), 6.80−6.77 (m, 1H), 6.64 (d, *J* = 2.5 Hz, 1H), 5.76 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 137.9, 132.4, 129.8, 129.0, 128.9, 127.1, 126.9, 119.5, 113.3, 112.3, 110.8, 105.7, 55.7; LRMS (EI, 70 eV) *m*/*z* (%): 280 (M$^+$, 100), 236 (37), 134 (32).

*3-Phenyl-7-(trifluoromethyl)-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3v**).* Yellow solid (25.7 mg, 40%); mp 74−75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.52 (m, 1H), 7.46−7.41 (m, 6H), 7.35 (s, 1H), 5.72 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 137.6, 131.9, 130.3, 129.7 (q, J_{C-F} = 33.3 Hz), 129.0, 127.4, 126.7, 125.3, 124.3, 123.2 (q, J_{C-F} = 267.8 Hz), 118.5, 109.5, 105.4; LRMS (EI, 70 eV) *m*/*z* (%): 318 (M$^+$, 100), 298 (17), 291 (18), 217 (25); HRMS (ESI): Calcd for $C_{16}H_{10}F_3N_2S^+$ ([M+H]$^+$): 319.0511, Found: 319.0519.

*7-Bromo-3-phenyl-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3w**).* Yellow solid (33.4 mg, 51%); mp 121−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.33 (m, 5H), 7.31−7.29 (m, 1H), 7.16−7.14 (m, 2H), 5.64 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 135.6, 132.0, 130.9, 130.1, 129.6, 129.0, 127.7, 127.3, 120.1, 119.7, 109.8, 105.5; LRMS (EI, 70 eV) *m*/*z* (%): 328/330 (M$^+$, 100), 249 (69), 222 (52), 125 (25); HRMS (ESI): Calcd for $C_{15}H_{10}BrN_2S^+$ ([M+H]$^+$): 328.9743, Found: 328.9746.

*7-Chloro-3-phenyl-4H-benzo[b][1,4]thiazine-4-carbonitrile (**3x**).*[5b] Yellow solid (31.9 mg, 56%); mp 112−113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.33 (m, 5H), 7.22−7.20 (m, 1H), 7.17−7.14 (m, 1H), 7.02−7.01 (m, 1H), 5.64 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 135.0, 132.7, 132.0, 130.1, 129.0, 128.0, 127.4, 127.3, 126.8, 119.4, 109.9, 105.4; LRMS (EI, 70 eV) *m*/*z* (%): 284 (M$^+$, 100), 249 (35), 222 (39), 125 (29).

*3-Phenyl-4H-benzo[b][1,4]thiazine-4-carboxamide (**4**).* Pale yellow solid (39.0 mg, 73%); mp 170−171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.53 (m, 1H), 7.48−7.47 (m, 2H), 7.31−7.21 (m, 5H), 7.14−7.11 (m, 1H), 6.75 (s, 1H), 5.00 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 139.8, 137.9, 135.2, 133.6, 129.2, 128.8, 127.22, 127.19, 127.06, 126.5, 125.1, 118.2; LRMS (EI, 70 eV) *m*/*z* (%): 268 (M$^+$, 23), 225 (100), 224 (45), 193 (21); HRMS (ESI): Calcd for $C_{15}H_{13}ON_2S^+$ ([M+H]$^+$): 269.0743, Found: 269.0753.

*3-Phenyl-4H-benzo[b][1,4]thiazine-4-carbonitrile 1,1-dioxide (**5**).*[13] White solid (51.7 mg, 92%); mp 130−131 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15−8.13 (m, 1H), 7.80−7.79 (m, 2H), 7.65−7.61 (m, 4H), 7.58−7.55 (m, 2H), 6.31 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 134.1, 133.8, 132.4, 130.7, 129.3, 128.9, 127.75, 127.65, 123.9, 117.9, 109.2, 106.0; LRMS (EI, 70 eV) *m*/*z* (%): 282 (M$^+$, 40), 218 (100), 190 (14), 105 (13).

*N-(2-Chlorophenyl)cyanamide (**7**).*[15] White solid (21.7 mg, 71%); mp 103−104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.28 (m, 1H), 7.24−7.19(m, 2H), 6.98−6.95 (m, 1H), 6.53 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.0, 129.7, 128.3, 124.3, 120.2, 116.0, 109.8; LRMS (EI, 70 eV) *m*/*z* (%): 152 (M$^+$, 100), 125 (36), 117 (21), 90 (22).

*N-Phenylcyanamide (**9**).*[15] White solid (17.8 mg, 75%); mp 43−44 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 129.7, 123.5, 115.4, 111.5; LRMS (EI, 70 eV) *m*/*z* (%): 118 (M$^+$, 100), 91 (90), 77 (25), 51 (19).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01668.

Copies of ^{1}H and ^{13}C NMR spectra for product **3a**−**3x**, **4**, **5**, **7**, and **9** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*zxg@wzu.edu.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (No. 21272177 and 21276200) and Zhejiang Provincial Natural Science Foundation of China (No. LR15B020002) for financial support.

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DOI: 10.1021/acs.joc.6b01668
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DOI: 10.1021/acs.joc.6b01668
J. Org. Chem. 2016, 81, 8647−8652