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One-Pot Synthesis of Benzimidazo[2,1-*b*]thiazoline Derivatives through an Addition/Cyclization/Oxidative Coupling Reaction

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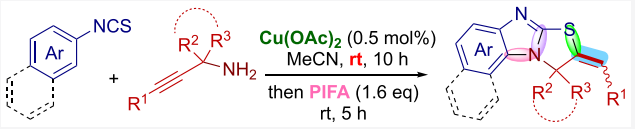
ABSTRACT: A novel and efficient approach to the synthesis of benzimidazo[2,1-*b*]thiazoline derivatives has been developed through an addition/cyclization/intramolecular oxidative C−H functionalization process. A variety of alkylene benzimidazo[2,1-*b*]thiazolines were conveniently assembled from the reaction of aryl isothiocyanate and propargylic amine in the presence of $Cu(OAc)_2$ and PIFA at room temperature. The product could be further converted to substituted benzimidazo[2,1-*b*]thiazole derivatives.



Nitrogen-containing heterocycle scaffolds wildly exist in a variety of natural products, pharmaceuticals, and agrochemicals.[1] Among them, benzimidazo[2,1-*b*]thiazoles have attracted great attention, because many of these *N*-heterocycles could be employed as antimicrobial,[2] anticancer,[3] anti-inflammatory,[4] and antiviral[5] agents. As a class of benzimidazo[2,1-*b*]thiazole derivatives, many alkylene benzimidazo[2,1-*b*]thiazolines possess biological and pharmaceutical activities. For example, it is claimed that some 2-substituted thiazolo[3,2-*a*]benzimidazol-3-ones (Figure 1A) have antitrichinellosis

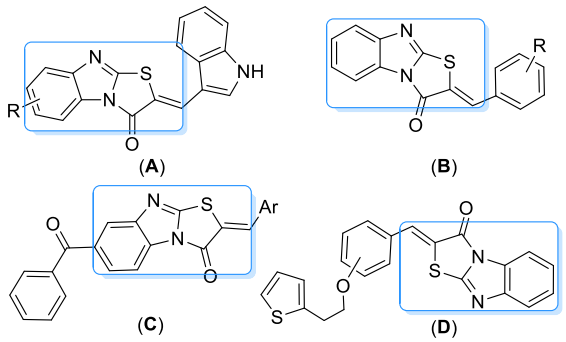


Figure 1. Some alkylene benzimidazo[2,1-*b*]thiazolines with biological activities.

activity.[6] Certain benzylidene benzimidazo[2,1-*b*]thiazolinones (Figure 1B) were studied as antifungal agents,[7] several thiazolobenzimidazole derivatives (Figure 1C) exhibit lipid peroxidation inhibition effects,[8] and some substituted benzimidazo[2,1-*b*]thiazolinones (Figure 1D) might have antidiabetic activity.[9]

General routes to benzimidazo[2,1-*b*]thiazoles involve the reactions of benzimidazole-2-thiols with α-halo carbonyl compounds,[4,8] propargyl bromides/tosylates,[10] or active alkynes.[11] Chen and co-workers developed a copper-catalyzed synthesis of benzimidazothiazoles through 1,2-aminothiolation of 1,1-dibromoalkenes.[12] Shen's group found that benzimidazothiazoles could be synthesized through Cu-catalyzed coupling reactions of *trans*-1,2-diiodoalkenes with benzimidazole-2-thiols.[13] Su et al. and Sun et al. individually reported the Cu-mediated assembly of benzimidazothiazoles via 1,2-aminothiolation of terminal alkynes.[14] Hajra and co-workers developed the synthesis of benzimidazo[2,1-*b*]thiazoles by Cu-catalyzed thioamination of nitroalkene.[15] The reaction of 2-aminothiazole with *o*-haloarylboronic acid or quinone is an alternative route to benzimidazo[2,1-*b*]thiazoles.[16] However, these methods may have some shortcomings such as the requirements of special starting materials (such as benzimidazole-2-thiols or 2-aminothiazoles) and/or relatively vigorous conditions (such as high temperatures). Moreover, until now, facile and selective access to 2-alkylene benzimidazo[2,1-*b*]thiazolines have been rarely documented.[7,8,11,17,18] These heterocycles were synthesized from the reactions of 2-mercaptobenzimidazoles, chloroacetic acids, and aryl aldehydes.[7,8,17] The reactions between *N*-(3-prop-2-yn-1-yl)-*o*-phenylenediamines and carbon disulfide/phenyl isothiocyante also provided the formation of 2-benzylidene benzimidazo[2,1-*b*]thiazolines.[18] However, the application scope may also be restricted, since benzimidazole-2-thiols or *N*-(prop-2-yn-1-yl)-*o*-phenylenediamines need to be prepared beforehand, and rigorous reaction conditions are employed (use of excess strong acids/bases at relatively high temperatures). Therefore, the devleopment of more convenient and versatile one-pot

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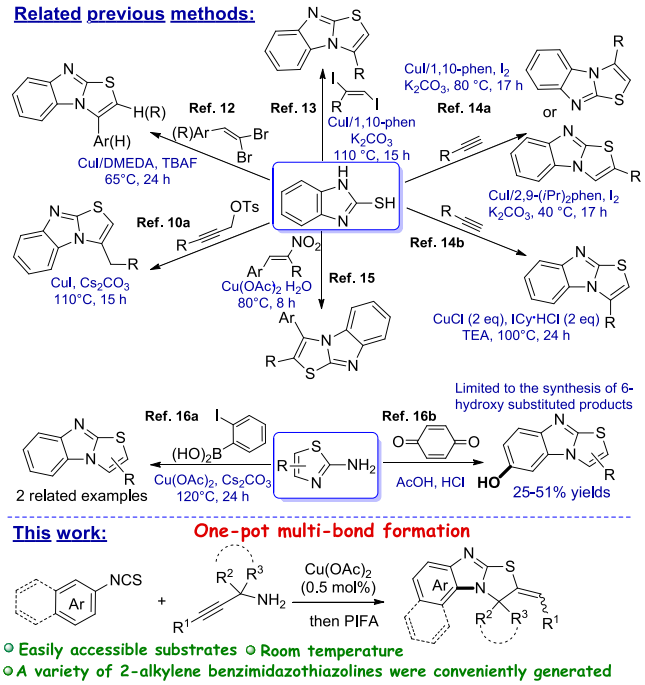
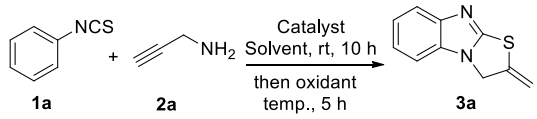
synthetic approaches to the assembly of 2-alkylene benzimidazo[2,1-*b*]thiazoline derivatives under milder conditions is still highly desired. In continuation of our ongoing efforts to developing novel one-pot multibond forming reactions for the assembly of heterocycles[19] and to overcome the inherent issues of the previously documented methods to the relevant heterocycles, herein we studied a novel and mild synthesis of 2-alkylene benzimidazo[2,1-*b*]thiazolines through an addition/cyclization/intramolecular oxidative coupling reaction of aryl isothiocyanate and propargylic amine in the presence of a copper(II) catalyst and a hypervalent iodine reagent. Compared with the previous protocols, the present method facilely generates a wide variety of 2-alkylene benzimidazo[2,1-*b*]thiazolines under milder conditions from easily accessible starting materials.

Scheme 1. Synthesis of Benzimidazo[2,1-*b*]thiazole Derivatives



To search for the feasibility of the hypothesized one-pot synthesis, we commenced our study with the reaction between phenyl isothiocyanate (**1a**) and propargylamine (**2a**) in the presence of 1 mol % CuI and 2 equiv of iodobenzene diacetate (PIDA) at rt for 10 h and then at 80 °C for 5 h. To our delight, the desired product 2-methylene-2,3-dihydrobenzo[4,5]-imidazo[2,1-*b*]thiazole **3a** was isolated in 42% yield (Table 1, entry 1). Its structure was unambiguously confirmed by X-ray diffraction analysis.[20] Different Cu catalysts were screened, and $Cu(OAc)_2$ was identified as the optimal catalyst (entries 1−4). A Ag catalyst was also tested, and it was inferior to $Cu(OAc)_2$ (entry 5). Interestingly, when the catalyst loading was reduced to 0.5 mol %, the yield was increased to 60% (entry 6). However, further decreasing the amount of the catalyst led to a lower efficiency (entry 7). A slightly higher yield could be obtained when the mixture was heated at 70 °C for the late stage (entry 8). The isolated yield was increased to 70% when the temperature was decreased to 65 °C (entry 9). However, further decreasing the temperature resulted in a lower yield (entry 10). Other solvents including THF, DMF,

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solv.	oxid.	T (°C)	yield[b]
1	CuI	MeCN	PIDA	80	42%
2	CuBr	MeCN	PIDA	80	33%
3	$Cu(OAc)_2$	MeCN	PIDA	80	51%
4	$Cu(OTf)_2$	MeCN	PIDA	80	50%
5	AgOTf	MeCN	PIDA	80	48%
6	$Cu(OAc)_2$	MeCN	PIDA	80	60%[c]
7	$Cu(OAc)_2$	MeCN	PIDA	80	55%[d]
8	$Cu(OAc)_2$	MeCN	PIDA	70	62%[c]
9	$Cu(OAc)_2$	MeCN	PIDA	65	70%[c]
10	$Cu(OAc)_2$	MeCN	PIDA	55	53%[c]
11	$Cu(OAc)_2$	THF	PIDA	65	45%[c]
12	$Cu(OAc)_2$	DMF	PIDA	65	trace[c]
13	$Cu(OAc)_2$	DMSO	PIDA	65	trace[c]
14	$Cu(OAc)_2$	dioxane	PIDA	65	trace[c]
15	$Cu(OAc)_2$/CuI[e]	MeCN	I_2	65	trace[c]
16	$Cu(OAc)_2$	MeCN	O_2[f]	65	trace[c]
17	$Cu(OAc)_2$	MeCN	IBX	65	trace[c]
18	$Cu(OAc)_2$	MeCN	PIFA	65	67%[c]
19	$Cu(OAc)_2$	MeCN	PIFA	rt	76%[c]
20	$Cu(OAc)_2$	MeCN	PIFA	rt	76%[c,g]
21	$Cu(OAc)_2$	MeCN	PIFA	rt	70%[c,h]

[a]Reaction conditions: phenyl isothiocyanate **1a** (0.5 mmol), propargylamine **2a** (0.51 mmol, 1.02 equiv), catalyst (1.0 mol %), in solvent (5 mL), under nitrogen, at rt for 10 h. Then, an oxidant (1.0 mmol, 2.0 equiv) was added, and the mixture was stirred at the indicated temperature for further 5 h. [b]Isolated yield. [c]0.5 mol % of Cu(II) catalyst was utilized. [d]0.2 mol % of Cu catalyst was utilized. [e]The ratio of $Cu(OAc)_2$ and CuI was 1:1. [f]An O_2 balloon was used. [g]1.6 equiv of PIFA was used. [h]1.2 equiv of PIFA was used.

DMSO, and dioxane were also tested, and MeCN gave the best result (compare entry 9 with entries 11−14). Other oxidative systems such as $Cu(OAc)_2$/CuI/I_2, $Cu(OAc)_2$/O_2, and IBX were unsuitable for this one-pot transformation (entries 15−17). However, switching the oxidant to PIFA afforded 67% yield of **3a** (entry 18). Notably, a good yield was achieved when the reaction was performed at room temperature (entry 19). Finally, different amounts of the hypervalent iodine reagent were also evaluated, indicating that 1.6 equiv of PIFA was appropriate for the reaction (entries 19−21).

Having established the optimal set of reaction conditions, we proceeded to examine the scope of isothiocyanates and propargylamines. The results are summarized in Table 2. The reactions of a range of aryl isothiocyantes **1** were investigated. It was found that aryl isothiocyanate bearing various substitution patterns afforded moderate to good yields of the desired tricyclic products (the synthesis of **3a**−**3i**). Both electron-donating (*p*-Me, *p*-*n*Bu, *o*-Me, 2,4-diMe, and *p*-MeO) and electron-withdrawing (*p*-Cl, *o*-Cl, and 2,4-diCl) groups on the aromatic ring of the isothiocyanates were well tolerated under these reaction conditions. The yield was slightly decreased when a substituent was introduced at the *ortho*-position of the phenyl ring (the synthesis of **3d**, **3g**, or **3h**). The reaction of the isothiocyanate with a *β*-naphthalenyl substituent furnished the desired tetracyclic product in a moderate yield (the synthesis of **3j**). The substrates bearing

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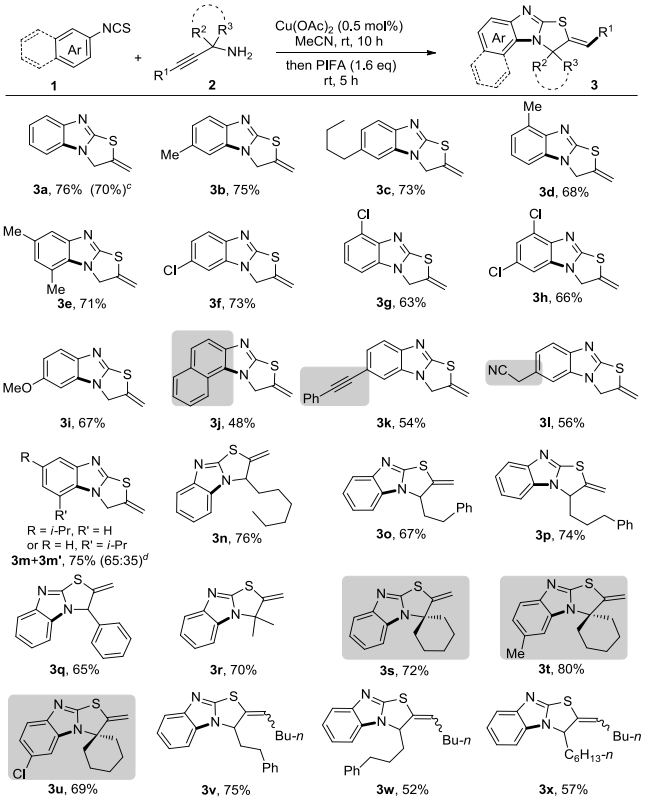
Table 2. One-Pot Synthesis of 2-Alkylene Benzimidazo[2,1-*b*]thiazoline Derivatives



[a]Reaction conditions: aryl isothiocyanate **1** (0.5 mmol), propargylamine **2** (0.51 mmol, 1.02 equiv), $Cu(OAc)_2$ (0.5 mol%), in MeCN (5 mL), under N_2, at rt for 10 h. Then, PIFA (0.8 mmol, 1.6 equiv) was added, and the mixture was stirred at rt for further 5 h. [b]Isolated yield. [c]The yield of a reaction on a 5 mmol scale is given in the parentheses. For details, see the Experimental Section. [d]The molecular ratio determined approximately by ^1H NMR is given in the parentheses.

functional groups such as phenylethynyl and cyanomethyl also smoothly participated in this one-pot transformation to give moderate yields of the desired products (the synthesis of **3k** and **3l**). When an *m*-substituted phenyl isothiocyanate was employed as the substrate, a mixture of two regioisomers was isolated (the synthesis of **3m** + **3m′**).

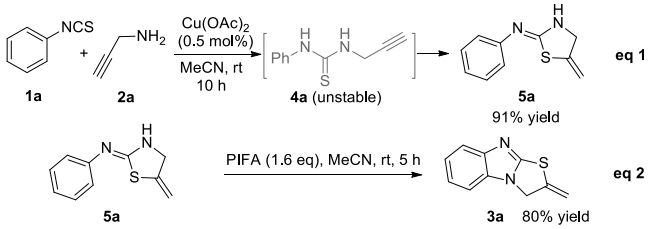
Next, we studied the generality of the one-pot transformation by using propargylic amines with different substituents. Moderate to good yields of the desired benzimidazothiazolines could be generated when α-monosubstituted or α-disubstituted propargylic amines were employed (the synthesis of **3n**−**3u**). It is noteworthy that spirocyclic benzimidazothiazoline derivatives were successfully constructed when 1-ethynylcyclohexanamine was utilized (the synthesis of **3s**−**3u**). The reactions with α,γ-disubstituted propargylamines also smoothly delivered the desired disubstituted 2-methylene benzimidazothiazolines **3v**−**3x**.

It is noteworthy that 2-alkylene benzimidazothiazoline-type product was obtained exclusively in each case, and no benzimidazothiazole that derived from the prototropic migration was observed under these conditions. Therefore, this transformation provides a highly selective assembly of 2-alkylene benzimidazo[2,1-*b*]thiazoline derivatives under very mild conditions.

A representative large-scale one-pot reaction was also carried out (Table 2, the synthesis of **3a**). The reaction proceeded smoothly on 5 mmol scale and gave the desired product in a good yield despite the requirement of a longer reaction time.

To probe the pathway of this transformation, two control experiments were performed (Scheme 2). The reaction of

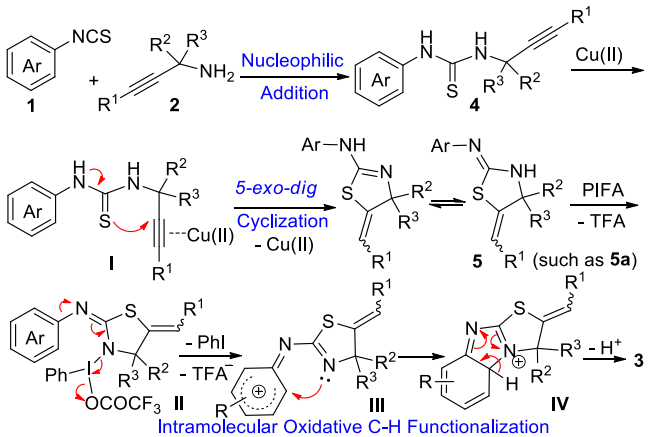
Scheme 2. Two Control Experiments



phenyl isothiocyanate (**1a**) and propargylamine (**2a**) under the catalysis of $Cu(OAc)_2$ (0.5 mol %) at rt afforded an excellent yield of the thiazolidine-type intermediate **5a** or its isomer (Scheme 2, eq 1). We failed to isolate the thiourea-type intermediate **4a** derived from the simple nucleophilic addition, since the intermediate seemed to be unstable under these conditions. In the presence of PIFA (1.6 equiv), the thiazolidine-type intermediate was smoothly converted to the product **3a** at rt (Scheme 2, eq 2).

Based on the above observation and the related reports,[21] a probable pathway for the one-pot synthesis of 2-alkylene benzimidazo[2,1-*b*]thiazolines is depicted in Scheme 3. First,

Scheme 3. Proposed Pathway for the One-Pot Synthesis



the nucleophilic addition of propargylamine **2** to isothiocyanate **1** led to the formation of *N*-proparyl thiourea-type intermediate **4**. Under the catalysis of Cu(II), an intramolecular 5-*exo*-*dig* cyclization afforded the corresponding intermediate **5**. **5** was converted to the final 2-alkylene benzimidazo[2,1-*b*]thiazoline **3** through an intramolecular oxidative coupling process in the presence of a hypervalent iodine reagent such as PIFA (possibly via intermediates **II**, **III**, and **IV**).

In order to demonstrate the synthetic utility of this method, product **3a** was further elaborated as depicted in Scheme 4. In the presence of DBU, **3a** was quantitatively converted to its isomer **6a**. Subsequently treated by bromine and reacted with a secondary aliphatic amine, benzimidazo[2,1-*b*]thiazol-2-yl amine **7** could be conveniently generated starting from this

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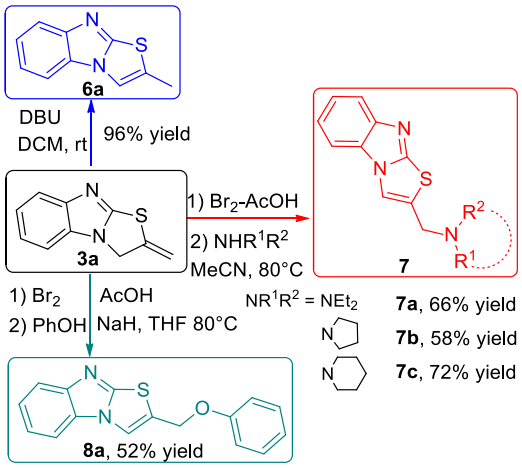
Scheme 4. Synthetic Application



molecule. 2-(Phenoxymethyl)benzimidazo[2,1-*b*]thiazole **8a** was successfully assembled after being treated with bromine-AcOH and phenol/NaH.

In conclusion, we have developed a novel and efficient strategy for the synthesis of benzimidazo[2,1-*b*]thiazoline derivatives. Catalyzed by Cu(II) (0.5 mol %) and in the presence of PIFA, a variety of alkylene benzimidazo[2,1-*b*]thiazolines were easily generated via an intermolecular addition/cyclization/intramolecular oxidative coupling process at room temperature. A broad range of aryl isothiocyanates and propargylic amines are compatible under these mild conditions. Furthermore, the obtained products could be further derived to corresponding substituted benzimidazo[2,1-*b*]-thiazoles conveniently. This modular and practical synthetic protocol will enable the synthesis of related *N*-heterocyclic molecules of biological and medicinal use.

EXPERIMENTAL SECTION

General Information. All one-pot reactions were carried out in an oven-dried Schlenk tube equipped with a magnetic stir bar under N_2 atmosphere. The solvents MeCN, DMF, and DMSO were distilled from CaH_2. THF and dioxane were distilled from Na. Substrates isothiocyanates **1**[22] and primary propargylamines **2**[23] were commercially available or prepared according to the known literature. All other reagents were obtained from commercial sources and utilized without further purification, if not stated otherwise. The heat source of all reactions that require heating is an oil bath. The NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a 400 or 600 MHz instrument with TMS as internal standard. Chemical shifts (δ) were reported in ppm with respect to TMS. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (J, Hz), and integration. TLC was carried out with 0.2 mm thick silica gel plates (GF254). Visualization was accomplished by UV light. The chromatographic columns were hand packed with silica gel 60 (160–200 mesh). HRMS analyses were carried out using a TOF-MS instrument with an ESI source.

General Procedure for the One-Pot Synthesis of Alkylene Benzimidazo[2,1-*b*]thiazolines 3. An oven-dried Schlenk tube was charged with a magnetic stir bar and $Cu(OAc)_2$ (0.0025 mmol, 0.5 mol %). The tube was capped and then evacuated and backfilled with nitrogen (3 times). A solution of propargylamine **2** (0.51 mmol, 1.02 equiv) in MeCN (2.5 mL) was added via syringe under nitrogen at room temperature. The mixture was stirred for 10 min. Then, a solution of aryl isothiocyanate **1** (0.5 mmol, 1 equiv) in MeCN (2.5 mL) was added slowly via syringe (for about 20 min), and the mixture was stirred at rt for about 10 h. Then, PIFA (0.8 mmol, 1.6 equiv) was added under the protection of nitrogen. The tube was sealed immediately, and the mixture was stirred at rt for 5 h. The mixture was diluted with DCM (10 mL) and washed with sat. $NaHCO_3$ (15 mL). The aqueous layer was extracted with DCM (10 mL × 3). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel using petroleum ether/AcOEt as an eluent to afford product **3**.

Procedure for the One-Pot Synthesis of Alkylene Benzimidazo[2,1-*b*]thiazoline 3a on a Larger Scale. An oven-dried two-necked flask was charged with a magnetic stir bar and $Cu(OAc)_2$ (0.025 mmol, 0.5 mol %). The tube was capped and then evacuated and backfilled with nitrogen (3 times). A solution of propargylamine **2** (5.1 mmol, 1.02 equiv) in MeCN (25 mL) was added via syringe under nitrogen at room temperature. The mixture was stirred for 10 min. Then, a solution of phenylisothiocyanate **1a** (5.0 mmol, 1 equiv) in MeCN (25 mL) was added slowly via syringe (for about 20 min), and the mixture was stirred at rt for about 12 h. Then, PIFA (8.0 mmol, 1.6 equiv) was added under the protection of nitrogen. The tube was sealed immediately, and the mixture was stirred at rt for 20 h. The mixture was diluted with DCM (100 mL) and washed with sat. $NaHCO_3$ (75 × 2 mL). The aqueous layer was extracted with DCM (100 mL × 3). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel using petroleum ether/AcOEt as an eluent to afford product **3a** as a yellow solid (0.656 g, 70% yield).

*2-Methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3a**).*[24] Yellow solid (72 mg, 76% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.19); mp 162–164 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67–7.61 (m, 1H), 7.23–7.17 (m, 3H), 5.54 (dd, J = 4.8, 2.4 Hz, 1H), 5.44 (dd, J = 5.2, 2.6 Hz, 1H), 4.96 (t, J = 2.4 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.2, 148.2, 141.5, 133.6, 122.3, 122.2, 119.1, 109.5, 108.8, 49.4; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{10}H_9N_2S$ 189.0481; found 189.0488.

*6-Methyl-2-methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]-thiazole (**3b**).* Yellow solid (76 mg, 75% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.21); mp 181.5–183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.2 Hz, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.93 (s, 1H), 5.49 (dd, J = 4.6, 2.3 Hz, 1H), 5.40 (dd, J = 5.2, 2.6 Hz, 1H), 4.83 (t, J = 2.4 Hz, 2H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.3, 146.1, 141.5, 133.6, 132.2, 123.4, 118.5, 109.3, 108.9, 49.1, 21.7; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{11}H_{11}N_2S$ 203.0637; found 203.0645.

*6-Butyl-2-methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]-thiazole (**3c**).* Light yellow solid (89 mg, 73% yield) (petroleum ether/EtOAc = 3:1, R_f = 0.48); mp 105–107 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, J = 8.2 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.97 (s, 1H), 5.51–5.48 (m, 1H), 5.42–5.38 (m, 1H), 4.88 (t, J = 2.1 Hz, 2H), 2.71–2.66 (m, 2H), 1.65–1.59 (m, 2H), 1.39–1.33 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.4, 146.3, 141.5, 137.4, 133.6, 122.9, 118.5, 109.3, 108.3, 49.2, 35.9, 34.3, 22.4, 14.1; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{17}N_2S$ 245.1107; found 245.1109.

*8-Methyl-2-methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]-thiazole (**3d**).* Light yellow solid (69 mg, 68% yield) (petroleum ether/EtOAc = 3:1, R_f = 0.45); mp 119.5–121 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.06 (t, J = 7.6 Hz, 1H), 7.02–6.96 (m, 2H), 5.51–5.48 (m, 1H), 5.40 (dd, J = 4.9, 2.4 Hz, 1H), 4.87 (t, J = 2.2 Hz, 2H), 2.60 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.1, 147.2, 141.5, 133.1, 128.9, 122.7, 122.1, 109.3, 106.3, 49.3, 16.7; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{11}H_{11}N_2S$ 203.0637; found 203.0638.

*5,7-Dimethyl-2-methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3e**).* Light yellow solid (77 mg, 71% yield) (petroleum ether/EtOAc = 3:1, R_f = 0.39); mp 196–198 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (s, 1H), 6.72 (s, 1H), 5.51–5.45 (m, 1H), 5.41–5.35 (m, 1H), 5.12–5.05 (m, 2H), 2.48 (s, 3H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.9, 148.5, 141.9, 131.9,

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131.3, 125.0, 119.0, 116.7, 108.9, 51.5, 21.5, 16.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{13}N_2S$ 217.0794; found 217.0795.

*6-Chloro-2-methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3f**).* Yellow solid (81 mg, 73% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.23); mp 203−204.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.49 (m, 1H), 7.17−7.15 (m, 2H), 5.55 (dd, J = 4.7, 2.3 Hz, 1H), 5.45 (dd, J = 7.8, 2.6 Hz, 1H), 4.92 (t, J = 2.4 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.1, 146.8, 140.8, 134.0, 128.0, 122.7, 119.8, 110.0, 109.0, 49.3; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{10}H_8ClN_2S$ 223.0091 (^{35}Cl); found 223.0102.

*8-Chloro-2-methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3g**).* Light yellow solid (70 mg, 63% yield) (petroleum ether/EtOAc = 3:1, R_f = 0.34); mp 145−147 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (d, J = 7.6 Hz, 1H), 7.09−6.95 (m, 2H), 5.54−5.50 (m, 1H), 5.43−5.38 (m, 1H), 4.91−4.87 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.1, 144.9, 140.8, 134.3, 123.3, 122.7, 122.2, 110.0, 107.5, 49.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{10}H_8ClN_2S$ 223.0091 (^{35}Cl); found 223.0094.

*6,8-Dichloro-2-methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3h**).* Light yellow solid (85 mg, 66% yield) (petroleum ether/EtOAc = 3:1, R_f = 0.41); mp 194.5−196.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.05 (s, 1H), 5.57−5.54 (m, 1H), 5.47−5.43 (m, 1H), 4.93−4.90 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.0, 143.8, 140.3, 134.3, 128.0, 123.8, 122.6, 110.4, 107.9, 49.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{10}H_7Cl_2N_2S$ 256.9702 (^{35}Cl, ^{35}Cl); found 256.9704.

*6-Methoxy-2-methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3i**).* Yellow solid (73 mg, 67% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.1); mp 156.5−158.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.8 Hz, 1H), 6.82 (dd, J = 8.8, 2.4 Hz, 1H), 6.69 (d, J = 2.3 Hz, 1H), 5.52 (dd, J = 4.5, 2.2 Hz, 1H), 5.43 (dd, J = 5.0, 2.5 Hz, 1H), 4.91 (t, J = 2.3 Hz, 2H), 3.84 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.2, 154.7, 142.6, 141.6, 134.1, 119.5, 110.3, 109.3, 93.6, 56.1, 49.2; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{11}N_2OS$ 219.0587; found 219.0591.

*9-Methylene-9,10-dihydronaphtho[2′,1′:4,5]imidazo[2,1-b]thiazole (**3j**).* Red brown solid (57 mg, 48% yield) (petroleum ether/EtOAc = 3:1, R_f = 0.43); mp 152−154 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79−7.74 (m, 3H), 7.73−7.68 (m, 1H), 7.44 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 5.26−5.22 (m, 1H), 5.16−5.12 (m, 1H), 4.64 (s, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 146.4, 140.3, 134.2, 130.5, 129.1, 127.8, 127.5, 126.5, 124.7, 121.6, 116.9, 104.6, 100.1, 48.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}N_2S$ 239.0637; found 239.0640.

*2-Methylene-6-(phenylethynyl)-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3k**).* White solid (78 mg, 54% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.39); mp 215−216 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 8.3 Hz, 1H), 7.55−7.51 (m, 2H), 7.41−7.37 (m, 2H), 7.37−7.31 (m, 3H), 5.57−5.54 (m, 1H), 5.47−5.44 (m, 1H), 4.95 (s, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.7, 148.3, 141.1, 133.4, 131.6, 128.5, 128.3, 126.3, 123.5, 119.1, 117.0, 112.0, 109.9, 90.1, 88.8, 49.4; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{13}N_2S$: 289.0794; found 289.0792.

*2-(2-Methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazol-6-yl)acetonitrile (**3l**).* White solid (64 mg, 56% yield) (petroleum ether/EtOAc = 2:1, R_f = 0.23); mp 167−168 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, J = 8.3 Hz, 1H), 7.23 (s, 1H), 7.09 (d, J = 7.0 Hz, 1H), 5.58 (dd, J = 4.8, 2.3 Hz, 1H), 5.47 (dd, J = 5.2, 2.6 Hz, 1H), 4.98 (t, J = 2.3 Hz, 2H), 3.87 (s, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.5, 147.9, 141.0, 133.9, 123.9, 122.2, 119.6, 118.3, 110.0, 108.3, 49.4, 23.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{10}N_3S$: 228.0590; found 228.0589.

*Mixture of 7-Isopropyl-2-methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3m**) and 5-Isopropyl-2-methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3m′**).* Mole ratio ≈ 65:35 (approximately determined by ^{1}H NMR). Light yellow solid (86 mg, 75% in total) (petroleum ether/EtOAc = 5:1, R_f = 0.26); mp 106−108 °C; **Major**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (d, J = 7.9 Hz, 1H), 7.08−7.04 (m, 2H), 5.53−5.50 (m, 1H), 5.20−5.15 (m, 2H), 4.87−4.85 (m, 1H), 3.39−3.32 (m, 1H), 1.34 (d, J = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.2, 148.2, 143.2, 131.1, 122.4, 118.3, 116.6, 108.9, 108.3, 51.9, 28.3, 24.0. **Minor**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.18−7.12 (m, 2H), 5.49−5.47 (m, 1H), 5.41−5.36 (m, 3H), 3.03−2.97 (m, 1H), 1.28 (d, J = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.9, 148.3, 141.5, 141.4, 131.8, 131.7, 121.0, 116.3, 109.3, 49.2, 34.2, 24.6.

*3-Hexyl-2-methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3n**).* Yellow oil (103 mg, 76% yield) (petroleum ether/EtOAc = 3:1, R_f = 0.59); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.20−7.13 (m, 2H), 5.44−5.42 (m, 1H), 5.41−5.38 (m, 1H), 5.23−5.18 (m, 1H), 2.23−2.17 (m, 1H), 1.93−1.87 (m, 1H), 1.43−1.35 (m, 1H), 1.23−1.13 (m, 6H), 1.07−1.00 (m, 1H), 0.80 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.3, 148.3, 146.1, 133.0, 122.0, 121.9, 119.1, 109.0, 108.8, 61.5, 34.6, 31.5, 28.9, 22.7, 22.5, 14.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{21}N_2S$ 273.1420; found 273.1422.

*2-Methylene-3-phenethyl-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3o**).* Yellow solid (98 mg, 67% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.27); mp 83.5−84.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.5, 1.6 Hz, 1H), 7.29−7.16 (m, 6H), 7.08 (d, J = 7.1 Hz, 2H), 5.59−5.54 (m, 1H), 5.53−5.50 (m, 1H), 5.33−5.27 (m, 1H), 2.80−2.71 (m, 1H), 2.63−2.54 (m, 1H), 2.43−2.35 (m, 1H), 2.32−2.22 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.2, 148.3, 145.8, 140.2, 132.8, 128.6, 128.2, 126.3, 122.2, 122.1, 119.2, 109.4, 108.7, 61.0, 36.2, 29.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{17}N_2S$ 293.1107; found 293.1112.

*2-Methylene-3-(3-phenylpropyl)-2,3-dihydrobenzo[4,5]imidazo-[2,1-b]thiazole (**3p**).* Yellow solid (113 mg, 74% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.28); mp 91−92.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 1H), 7.26−7.13 (m, 6H), 7.05 (d, J = 7.3 Hz, 2H), 5.45−5.38 (m, 2H), 5.27−5.21 (m, 1H), 2.61−2.53 (m, 2H), 2.31−2.24 (m, 1H), 1.99−1.93 (m, 1H), 1.81−1.73 (m, 1H), 1.46−1.38 (m, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.3, 148.4, 146.0, 141.1, 133.0, 128.5, 128.4, 126.1, 122.1, 122.0, 119.2, 109.2, 108.8, 61.4, 35.2, 33.8, 24.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{19}N_2S$ 307.1263; found 307.1260.

*2-Methylene-3-phenyl-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3q**).* Yellow solid (86 mg, 65% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.27); mp 121.5−123 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, J = 8.1 Hz, 1H), 7.42−7.37 (m, 3H), 7.33−7.28 (m, 2H), 7.15 (t, J = 7.4 Hz, 1H), 6.98 (t, J = 7.7 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.01 (d, J = 2.2 Hz, 1H), 5.45−5.40 (m, 1H), 5.27−5.22 (m, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.2, 148.5, 146.8, 137.4, 133.2, 130.1, 129.4, 127.3, 122.2, 122.0, 119.1, 111.4, 109.4, 65.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}N_2S$ 265.0794; found 265.0781.

*3,3-Dimethyl-2-methylene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3r**).* Brown oil (76 mg, 70% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.61 (m, 1H), 7.38−7.33 (m, 1H), 7.22−7.12 (m, 2H), 5.40 (d, J = 2.9 Hz, 1H), 5.32 (d, J = 2.9 Hz, 1H), 1.81 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.9, 152.4, 148.7, 132.3, 121.9, 121.6, 119.2, 108.6, 107.1, 65.3, 27.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{13}N_2S$ 217.0794; found 217.0799.

*2-Methylene-2H-spiro[benzo[4,5]imidazo[2,1-b]thiazole-3,1′-cyclohexane] (**3s**).* Yellow solid (92 mg, 72% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.0.35); mp 99−100.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.20−7.13 (m, 2H), 5.74 (d, J = 2.9 Hz, 1H), 5.36 (d, J = 2.9 Hz, 1H), 2.40 (td, J = 13.7, 4.9 Hz, 2H), 2.13−2.09 (m, 2H), 1.93−1.75 (m, 5H), 1.49−1.41 (m, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 153.3, 151.1, 148.9, 132.2, 121.8, 121.4, 119.3, 109.9, 109.2, 67.1, 34.0, 24.4, 21.7; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{17}N_2S$ 257.1107; found 257.1113.

*6-Methyl-2-methylene-2H-spiro[benzo[4,5]imidazo[2,1-b]thiazole-3,1′-cyclohexane] (**3t**).* Light yellow oil (108 mg, 80% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.46); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, J = 8.1 Hz, 1H), 7.22 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 5.74 (d, J = 1.6 Hz, 1H), 5.35 (d, J = 1.7 Hz, 1H), 2.47 (s, 3H), 2.40 (td, J = 13.6, 4.4 Hz, 2H), 2.14−2.08 (m, 2H), 1.95−1.77 (m, 5H), 1.53−1.44 (m, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 152.6,

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151.3, 147.0, 132.4, 131.2, 123.2, 118.8, 109.8, 109.4, 67.0, 33.9, 24.5, 21.9, 21.7; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{19}N_2S$ 271.1263; found 271.1269.

*6-Chloro-2-methylene-2H-spiro[benzo[4,5]imidazo[2,1-b]-thiazole-3,1′-cyclohexane] (**3u**).* Yellow solid (100 mg, 69% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.51); mp 121−122.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 1.3 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 5.74 (d, J = 2.6 Hz, 1H), 5.35 (d, J = 2.6 Hz, 1H), 2.30 (td, J = 13.7, 4.6 Hz, 2H), 2.11−2.06 (m, 2H), 1.93−1.85 (m, 3H), 1.81−1.73 (m, 2H), 1.48−1.40 (m, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 154.2, 150.5, 147.5, 132.6, 127.0, 122.3, 119.8, 110.3, 109.3, 67.2, 33.9, 24.3, 21.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{16}ClN_2S$ 291.0717 (^{35}Cl); found 291.0725.

*2-Pentylidene-3-phenethyl-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (**3v**).* Light yellow oily liquid (131 mg, 75% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.48); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, J = 7.9 Hz, 1H), 7.27−7.16 (m, 6H), 7.11−7.02 (m, 2H), 5.88−5.80 (m, 1H), 5.32−5.17 (m, 1H), 2.72 (td, J = 13.4, 5.2 Hz, 1H), 2.58−2.51 (m, 1H), 2.43−2.36 (m, 1H), 2.30−2.11 (m, 3H), 1.62−1.50 (m, 2H), 1.47−1.40 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.4, 148.4, 140.4, 136.8, 132.9, 128.5, 128.2, 126.2, 125.0, 122.0, 121.9, 119.1, 108.7, 60.4, 36.6, 31.1, 30.9, 29.1, 22.3, 14.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{25}N_2S$ 349.1733; found 349.1738.

*2-Pentylidene-3-(3-phenylpropyl)-2,3-dihydrobenzo[4,5]-imidazo[2,1-b]thiazole (**3w**).* Yellow oily liquid (95 mg, 52% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.36); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70−7.62 (m, 1H), 7.23 (t, J = 7.4 Hz, 2H), 7.21−7.19 (m, 1H), 7.18−7.17 (m, 1H), 7.16−7.12 (m, 2H), 7.09−7.02 (m, 2H), 5.69 (td, J = 7.2, 1.4 Hz, 1H), 5.25−5.17 (m, 1H), 2.56 (t, J = 7.4 Hz, 2H), 2.27−2.20 (m, 1H), 2.19−2.07 (m, 2H), 1.95−1.88 (m, 1H), 1.78−1.70 (m, 1H), 1.48−1.34 (m, 5H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.6, 148.4, 141.3, 136.9, 133.0, 128.5, 128.4, 126.1, 124.8, 122.0, 121.9, 119.2, 108.8, 60.8, 35.3, 34.2, 31.1, 30.9, 24.2, 22.4, 14.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{27}N_2S$ 363.1889; found 363.1888.

*3-Hexyl-2-pentylidene-2,3-dihydrobenzo[4,5]imidazo[2,1-b]-thiazole (**3x**).* Yellow oily liquid (94 mg, 57% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.48); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, J = 7.8 Hz, 1H), 7.27−7.25 (m, 1H), 7.21−7.12 (m, 2H), 5.81−5.67 (m, 1H), 5.28−5.16 (m, 1H), 2.23−2.10 (m, 3H), 1.94−1.84 (m, 1H), 1.50−1.44 (m, 2H), 1.41−1.34 (m, 3H), 1.25−1.15 (m, 6H), 1.08−1.01 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.6, 148.5, 137.2, 133.1, 124.7, 122.0, 121.8, 119.2, 108.9, 61.1, 35.1, 31.6, 31.1, 31.0, 29.1, 22.9, 22.6, 22.4, 14.07, 13.98; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{29}N_2S$ 329.2046; found 329.2045.

Procedure for the Synthesis of the Intermediate 5a. An oven-dried Schlenk tube was charged with a magnetic stir bar and $Cu(OAc)_2$ (0.0025 mmol, 0.5 mol %). The tube was capped and then evacuated and backfilled with nitrogen (three times). A solution of propargylamine **2a** (0.51 mmol, 1.02 equiv) in MeCN (2.5 mL) was added via syringe under nitrogen at room temperature. The mixture was stirred for 10 min. Then, a solution of phenyl isothiocyanate **1a** (0.5 mmol, 1 equiv) in MeCN (2.5 mL) was added slowly via syringe (for about 20 min), and the mixture was stirred at rt for about 10 h. The mixture was diluted with DCM (10 mL) and washed with sat. $NaHCO_3$ (15 mL). The aqueous layer was extracted with DCM (10 mL × 3). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel using petroleum ether/AcOEt as an eluent to afford intermediate **5a**.

*5-Methylene-N-phenyl-4,5-dihydrothiazol-2-amine **5a**.*[25] Yellow solid (87 mg, 91% yield) (petroleum ether/EtOAc = 5:1, R_f = 0.44); mp 101−102.5 °C (lit.[23] mp 104−108 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (t, J = 7.8 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.07 (t, J = 7.4 Hz, 1H), 5.20−5.18 (m, 1H), 5.12 (dd, J = 4.0, 2.2 Hz, 1H), 4.57−4.53 (m, 2H) (the signal of NH is missing); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 159.4, 145.7, 143.9, 129.1, 123.6, 121.3, 104.2, 58.4.

Procedure for the Synthesis of Benzimidazo[2,1-*b*]thiazole 6a. DBU (0.2 mmol) in DCM (2 mL) was added dropwise to a solution of product **3a** (0.5 mmol) in DCM (3 mL) at 0 °C. Then, the mixture was stirred at rt for about 5 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using petroleum ether/AcOEt as an eluent to afford product **6a**.

*2-Methylbenzo[4,5]imidazo[2,1-b]thiazole (**6a**).*[16a] Light yellow solid (90 mg, 96% yield) (petroleum ether/EtOAc = 3:1, R_f = 0.27); mp 160.5−162 °C (lit.[16a] mp 156−159 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.24 (s, 1H), 7.18 (t, J = 7.5 Hz, 1H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.5, 147.5, 129.5, 124.6, 123.0, 120.7, 119.0, 113.8, 110.0, 14.1.

General Procedure for the Synthesis of Benzimidazo[2,1-*b*]thiazolylmethyl Amine Derivatives 7. An oven-dried flask equipped with a condenser was charged with a magnetic stir bar, **3a** (1.0 mmol) and glacial acetic acid (2 mL). The flask was capped. Then, a solution of bromine (176 mg, 1.1 mmol) in acetic acid (2 mL) was added dropwise via syringe at rt. The mixture was stirred at 80 °C for about 2 h. The reaction was quenched by the addition of sat. $NaHCO_3$ solution, and the mixture was extracted with DCM (5 mL × 3). The solid was washed with water, dried, and utilized for the next step without further purification.

An oven-dried Schlenk tube was charged with a magnetic stir bar and the above bromide (53 mg, 0.2 mmol). The tube was capped and then evacuated and backfilled with nitrogen (three times). MeCN (1 mL) was added via syringe at rt. The reaction mixture was stirred for about 10 min at rt, and then, a solution of amine (0.6 mmol, 3 equiv) in MeCN (1 mL) was added dropwise. After being stirred at room temperature for about 3 h, the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 10:1) to give product **7**.

*N-(Benzo[4,5]imidazo[2,1-b]thiazol-2-ylmethyl)-N-ethylethanamine (**7a**).* Light yellow solid (34 mg, 66% yield) (petroleum ether/EtOAc = 3:1, R_f = 0.1); mp 78.5−80.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.53 (s, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 3.72 (s, 2H), 2.61 (q, J = 7.1 Hz, 4H), 1.07 (t, J = 7.1 Hz, 6H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.0, 147.7, 130.7, 129.6, 123.2, 120.8, 119.2, 114.0, 110.1, 50.9, 46.7, 11.9; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{18}N_3S$ 260.1216; found 260.1217.

*2-(Pyrrolidin-1-ylmethyl)benzo[4,5]imidazo[2,1-b]thiazole (**7b**).* Yellow oil (30 mg, 58% yield) (petroleum ether/EtOAc = 4:1, R_f = 0.4). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 3.80 (s, 2H), 2.60−2.54 (m, 4H), 1.77−1.72 (m, 4H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 156.3, 147.5, 129.9, 129.1, 123.4, 121.1, 118.8, 116.4, 111.7, 53.8, 52.9, 23.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{16}N_3S$ 258.1059; found 258.1060.

*2-(Piperidin-1-ylmethyl)benzo[4,5]imidazo[2,1-b]thiazole (**7c**).* Yellow oil (39 mg, 72% yield) (petroleum ether/EtOAc = 1:1, R_f = 0.4). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 3.60 (s, 2H), 2.55−2.40 (m, 4H), 1.63−1.57 (m, 4H), 1.49−1.41 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.1, 147.8, 129.6, 129.4, 123.3, 120.9, 119.3, 114.3, 110.1, 56.6, 54.5, 26.0 24.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{18}N_3S$ 272.1216; found 272.1219.

General Procedure for the Synthesis of 2-(Phenoxymethyl)-benzo[4,5]imidazo[2,1-*b*]thiazole 8a. An oven-dried Schlenk tube was charged with a magnetic stir bar and phenol (19 mg, 0.2 mmol). The tube was capped and then evacuated and backfilled with nitrogen (three times). Anhydrous THF (2 mL) was added via syringe. The reaction mixture was stirred for about 10 min at rt, and then, sodium hydride (240 mg, 10 mmol) was added immediately under the protection of nitrogen. The tube was capped again, and the mixture was stirred at rt for about 1 h. After that, a solution of the above bromide (53 mg, 0.2 mmol) in anhydrous THF (1 mL) was added

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dropwise. After being stirred at rt for 16 h, the solvent was removed in vacuo, and the residue was dissolved in DCM (20 mL), washed with brine (5 mL × 2), and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 10:1) to give the product as a yellow solid.

*2-(Phenoxymethyl)benzo[4,5]imidazo[2,1-b]thiazole (**8a**).* Yellow solid (29 mg, 52% yield) (petroleum ether/EtOAc = 2:1, R_f = 0.4); mp 158−158.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 7.9 Hz, 1H), 7.74 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.40−7.32 (m, 3H), 7.28 (d, J = 7.7 Hz, 1H), 7.07−6.95 (m, 3H), 5.20 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 157.8, 156.7, 133.2, 129.9, 128.5, 125.2, 123.8, 122.2, 121.4, 119.5, 116.2, 115.3, 110.3, 64.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}N_2OS$ 281.0743; found 281.0744.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01137.

Copies of ^{1}H NMR and ^{13}C NMR spectra for the products (**3**), the derivatives (**6a**, **7**, and **8a**), and key intermediate (**5a**) and crystallographic information for of **3a** (PDF)

Crystal structure of **3a** (CIF)

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Notes

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