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Access to Thiazole via Copper-Catalyzed [3+1+1]-Type Condensation Reaction under Redox-Neutral Conditions

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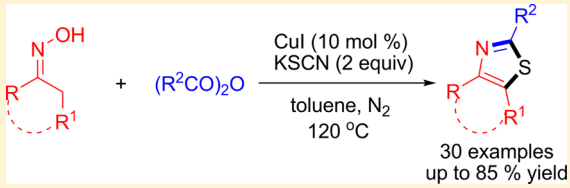
Supporting Information

ABSTRACT: A new strategy for thiazoles via copper-catalyzed [3+1+1]-type condensation reaction from oximes, anhydrides and potassiumthiocyanate (KSCN) is developed herein. The transformation has good functional group tolerance and various thiazoles were formed smoothly in good to excellent yields under mild reaction conditions. This process involves copper-catalyzed N−O/C−S bond cleavages, activation of vinyl sp^2 C−H bond, and C−S/C−N bond formations which are under redox-neutral conditions as well as operational simplicity.

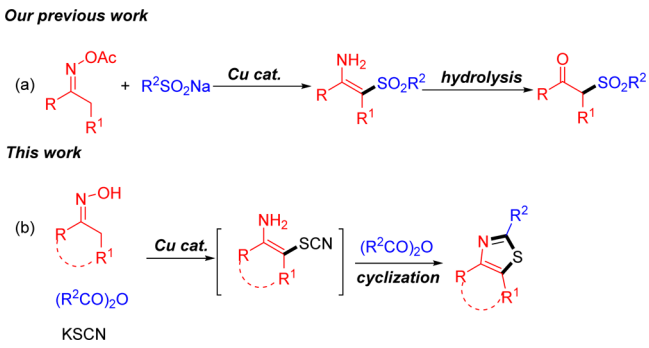


The thiazole ring systems are widely located in natural products and pharmaceuticals.[1] Until now, there are some methods for the synthesis of thiazoles. The classical method is well-known Hantzsch reaction, which is the condensation of thioamide with α-haloketones.[2] However, the synthesis of α-haloketone involves halogenation of ketone that causes environmental pollution. Analogously, the epoxides and propargylic alcohols are also used for the synthesis of thiazoles with thioamide.[3] Other ways to build thiazole ring has also been reported. Banert et al. reported a method for thiazoles via coupling of allenyl isothiocyanates with nucleophiles.[4a] Sheldrake and McDonald et al. illustrated the reaction of *N*,*N*-diformylaminomethyl aryl ketones and phosphorus pentasulfide to produce 5-arylthiazole.[4b] In addition, thiazoles could be synthesized by iron or palladium-catzlyzed reactions of vinyl azides with potassium thiocyanate.[4c,d] However, all these methods have some limitations, such as nonavailability of raw materials, poor functional group tolerance, and the use of equivalent amount of oxidants.

Oximes are widely used for the construction of amides and nitriles.[5] In addition, they were widely employed for preparing the nitrogen-bearing heterocyclic compounds via S_N2 reaction,[6] radical cyclization.[7] In the late 20th century, Narasaka et al. seminally studied palladium-catalyzed intramolecular Heck-type amination and copper-catalyzed cyclization of oxime derivatives.[8] Recently, more and more chemists gave their attentions to the transition-metal catalyzed C−H functionalization with oxime derivatives served as both reactants and internal oxidants.[9] These reactions using internal oxidants have many advantages such as mild reaction conditions, high selectivity and good functional group tolerance. More and more transformations about oxime and its derivatives have been realized by rhodium,[10] ruthenium,[11] palladium,[12] and copper.[13]

In recent years, we focused on the transformations of oxime and its derivatives.[14] In our previous work, we developed a copper-catalyzed synthesis of sulfone derivatives via the sulfonylation of oxime acetates with sodium sulfinates. The β-sulfonylvinylamines could be obtained in good yields and β-ketosulfones could also be efficiently generated upon hydrolysis by silica gel (Scheme 1a).[14a] Herein, we disclose a novel method for thiazoles via copper-catalyzed [3+1+1]-cyclization reaction from oximes, anhydrides, and potassium thiocyanate (Scheme 1b).

Scheme 1. Our Previous Work and This Work



At the start of our studies, we used acetophenone oxime (**1a**) and acetic anhydride (**2a**) as model substrates to screen catalysts, solvents, and sulfur sources and the results were summarized in Table 1. Initial attempts were performed with a catalytic amount of CuI, potassium thiocyanate (KSCN) as sulfur sources, and DCE as solvent under N_2 atmosphere. We were excited that the product 2-methyl-4-phenylthiazole (**3a**) was obtained in 33% GC yield (Table 1, entry 1). Various solvents, such as 1,4-dioxane, CH_3CN, and toluene, were examined (entries 2−4). To our delight, toluene gave a satisfactory yield (81% GC yield). Different copper salts, such as CuCl, CuBr, $CuBr_2$, $Cu(OAc)_2$, and $Cu(OTf)_2$, could also catalyze this reaction, but none of them were found to be more efficient than CuI (entries 5−9). Iron salts also showed the

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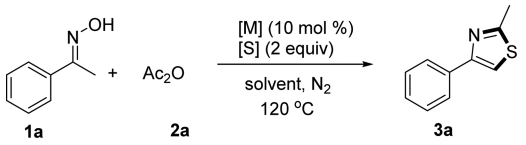
Table 1. Optimization of the Reaction Conditions[a]



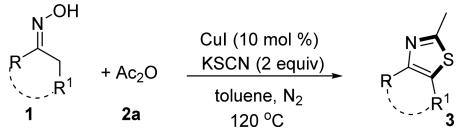
entry	[M]	solvent	[S]	yield[b] (%)
1	CuI	DCE	KSCN	33
2	CuI	1,4-dioxane	KSCN	15
3	CuI	CH_3CN	KSCN	42
4	**CuI**	**toluene**	KSCN	**81 (73)**
5	CuCl	toluene	KSCN	68
6	CuBr	toluene	KSCN	72
7	$CuBr_2$	toluene	KSCN	73
8	$Cu(OAc)_2$	toluene	KSCN	75
9	$Cu(OTf)_2$	toluene	KSCN	60
10	$Fe(OAc)_2$	toluene	KSCN	70
11	$FeBr_2$	toluene	KSCN	50
12	$FeBr_3$	toluene	KSCN	47
13	$FeCl_3$	toluene	KSCN	55
14	$PdCl_2$	toluene	KSCN	n.d.
15	AgCl	toluene	KSCN	n.d.
16	CuI	toluene	NaSCN	46
17	CuI	toluene	NH_4SCN	n.d.
18	CuI	toluene	S	n.d.
19	CuI	toluene	Na_2S	n.d.

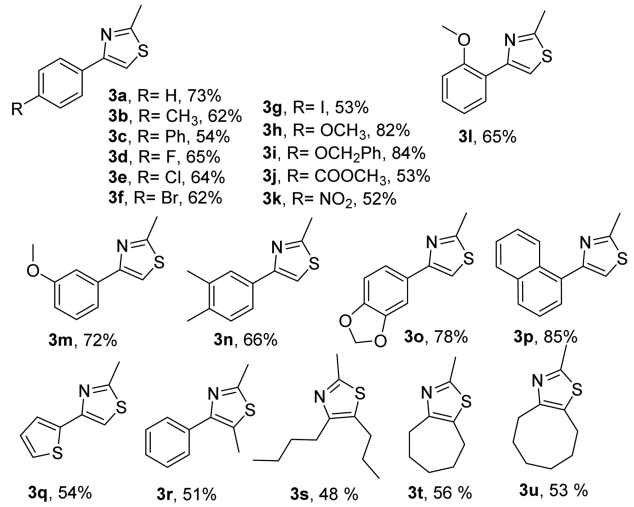
[a]Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (1.5 mmol), [S] (1.0 mmol), [M] (10 mol%), in solvent (3 mL) at 120 °C under N_2 for 24 h. [b]Determined by GC and dodecane as internal standard. Number in parentheses is yield of isolated product. n.d. = not detected.

catalytic activity in this transformation (entries 10−13). However, when other metals, such as $PdCl_2$ and AgCl, were used as catalysts, no products were obtained (entries 14−15). Other sulfur sources, such as NaSCN, NH_4SCN, S, and Na_2S, were screened, and except NaSCN could afford the product in 46% GC yield, while others did not form the product (entries 16−19). Thus, the optimal catalytic system for this copper-catalyzed [3+1+1]-type cyclization reaction was **1a** (0.5 mmol), **2a** (1.5 mmol), KSCN (1.0 mmol), CuI (10 mol%), in toluene (3 mL) at 120 °C under N_2 for 24 h.

With the optimized reaction conditions in hand, the generality of this copper-catalyzed [3+1+1]-type condensation reaction of oximes, anhydrides, and potassium thiocyanate (KSCN) was examined. The scope of the oximes was first explored by the adoption of acetic anhydride as the coupling partner, and the results were summarized in Table 2. Both electron-rich and electron-poor para-substituted acetophenone oximes participated in good yields (**3a−3k**). In addition, the substrates with methoxy at the *meta*- or *ortho*-position could also react smoothly to afford the corresponding products in good yields (**3l−3m**). On the whole, acetophenone oximes with an electron-donating group showed higher reactivity than those with an electron-withdrawing group. It is worth noting that the disubstituted acetophenone oximes were also suitable substrates, and the corresponding products were formed in 66% and 78% yields, respectively (**3n−3o**). Notably, the reactions of other aromatic ring oximes were also performed smoothly and afforded the corresponding products in 85% and 54% yields (**3p−3q**). Propiophenone oxime was available for the construction of 2,4,5-substituted thiazoles in 51% yield (**3r**).

Table 2. Cu(I)-Catalyzed Synthesis of Thiazoles from Various Oxime and Acetic Anhydride[a,b]





[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.5 mmol), KSCN (1.0 mmol), CuI (10 mol%), toluene (3.0 mL), under N_2 at 120 °C for 24 h. [b]Isolated yield based on **1**.

It was worth mentioning that alkyl oximes were also suitable for this transformation and moderate yields could be obtained (**3s−3u**).

Next, the scope of anhydrides was examined in this reaction (Table 3). For various alkyl anhydrides, including propionic, butyric, isobutyl, trimethylacetic, and cyclohexanecarboxylic anhydrides, the reactions proceeded smoothly to afford the desired products **3v−3z** in good yields. However, benzoic anhydride could not undergo the transformation and acetophenone oxime was converted to acetophenone.

In order to further expand our methods, we used 1-tetralone oximes to synthesize the corresponding thiazoles, which could be obtained in moderate yields (**4a−d**) (Scheme 2) by further oxidation with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).

In order to understand more clearly about the reaction mechanism, some control experiments were performed (Scheme 3). When we directly used oxime acetate as the substrate, the yield of **3a** was 69%. In this case, two equivalents of acetic anhydride was used [eq (1)]. When the radical trapping reagent (BHT) was added to the reaction system, no products were detected, which suggested a radical process might be involved in this transformation [eq (2)]. In addition, when 1,1-diphenylethylene was added in our standard conditions, the product **3a** was obtained in 65% yield and 1,1-diphenylethylene did not participate in the reaction. This control experiment showed that no stable free radical was formed in the reaction [eq (3)]. The reaction was also good with (*Z*)-acetophenone oxime, which can prove this reaction not to be a S_N2-type process [eq (4)]. Further, we utilized sodium thiophenoxide to capture the free radical produced by reduction of oxime acetate, however, no cross-coupling product was generated, while acetophenone and 1,2-diphenyldisulfane were obtained instead [eq (5)]. When the reaction was

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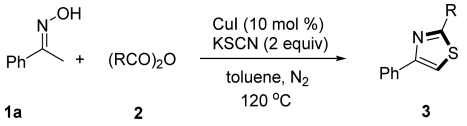
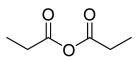
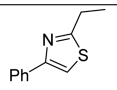
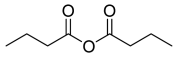
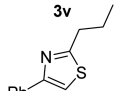
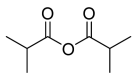
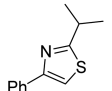
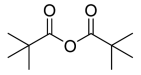
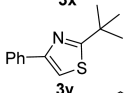
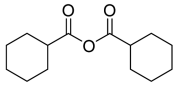
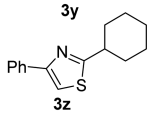
Table 3. Cu(I)-Catalyzed Synthesis of Thiazoles from Acetophenone Oxime and Various Anhydride[a,b]

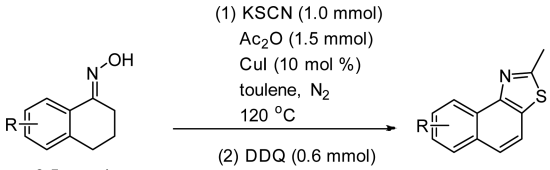


1a 2 3

Entry	Acid anhydride	Product	Yield
1		 **3v**	72%
2		 **3w**	63%
3		 **3x**	73%
4		 **3y**	74%
5		 **3z**	78%

[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), KSCN (1.0 mmol), CuI (10 mol%), toluene (3.0 mL), under N_2 at 120 °C for 24 h. [b]Isolated yield based on **1a**.

Scheme 2. Synthesis of Naphtho[1,2-*d*]thiazoles from 1-Tetralone Oximes

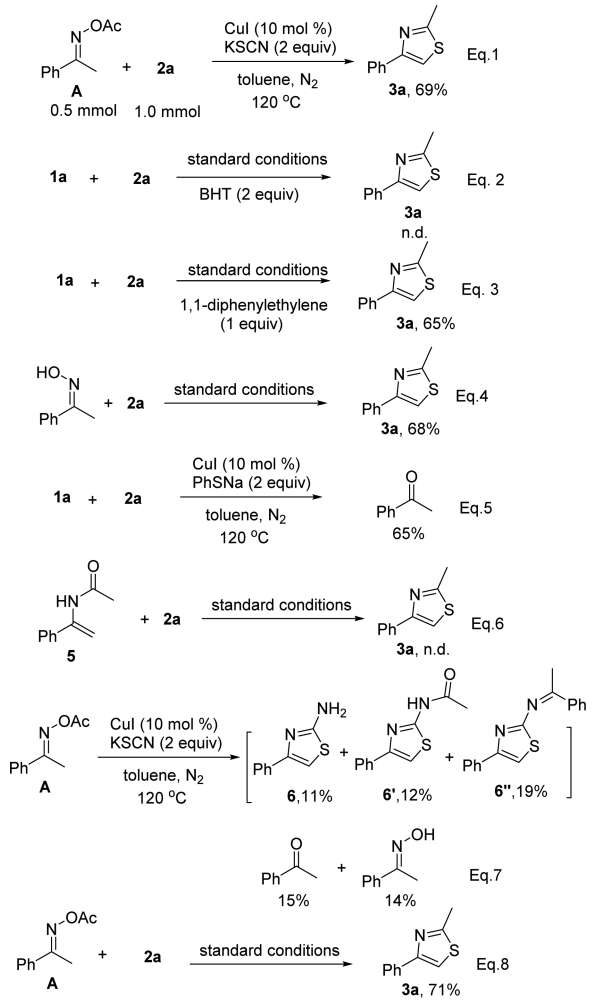


4a, R= H, 58%
4b, R= 7-OCH_3, 54%
4c, R= 8-OCH_3, 52%
4d, R= 8-Br, 48%

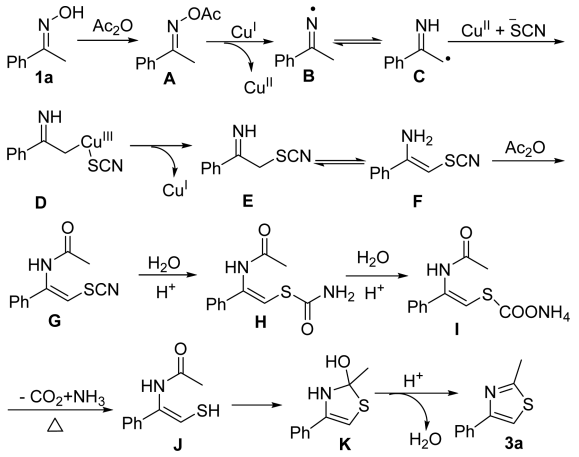
performed with compound **5** under the standard conditions, the product **3a** was not detected [eq (6)]. Therefore, compound **5** could be ruled out as the major intermediate in the transformation. Furthermore, when the reaction of oxime acetate **A** with KSCN was performed in the presence of CuI but in the absence of acetic anhydride, 4-phenylthiazol-2-amine (**6**) was formed. And the amine (**6**) was further converted to compound **6′** and **6″** via the reaction with acetic acid or acetophenone generated in situ [eq (7)]. When we subjected intermediate **A** to the standard conditions, the product **3a** was formed in 71% yield [eq (8)].

Based on the control experiments and previous reports,[13,14] a possible mechanism was proposed in Scheme 4. Oxime acetate **A** is first generated from the acylation of acetophenone ketoxime. Therewith, the imine-free radical **B** is formed from **A** by single-electron transfer (SET) reduction with CuI.[13d,e,14] The intermediate **B** is quickly isomerized to intermediate **C**,[13e] and trapping of intermediate **C** with Cu^{II} and thiocyanate anion provides alkyl-Cu^{III} intermediate **D**.[13f] Intermediate **E** is formed via reductive elimination of Cu(I) from intermediate **D**.[13f] After isomerization and acylation process, intermediate **G** would be

Scheme 3. Mechanistic Studies



Scheme 4. Proposed Mechanism



obtained. Subsequently, intermediate **I** is generated by two-step hydrolytic process under acidic conditions. Intermediate **J** is formed by losing carbon dioxide and ammonia of intermediate **I** under heating conditions. Finally, the intramolecular nucleophilic attack of intermediate **J**, followed by intramolecular dehydration to give product **3a**.

In conclusion, an efficient and novel synthesis of thiazoles via copper-catalyzed [3+1+1]-type reaction from oximes, anhy-

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dride, and KSCN has been developed. Furthermore, the reaction was accomplished through N−O/C−S bond cleavages, and new C−S/C-N bond formations, along with the activation of vinyl sp^2 C−H bond. Most of all, this transformation was realized under redox-neutral conditions which provides a new way for the construction of thiazoles from oximes.

EXPERIMENTAL SECTION

General Information. Melting points were measured with a melting point instrument and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a 400 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.26 and 77.0 ppm, respectively, and chloroform was used as the solvent with TMS as the internal standard. GC-MS was obtained using electron ionization. HRMS was obtained with a LCMS-IT-TOF mass spectrometer. TLC was performed by using commercially prepared 100−400 mesh silicagel plates, and visualization was effected at 254 nm. IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with an infrared Fourier spectrometer. High-resolution mass spectra (ESI) were obtained with a LCMS-ITTOF mass spectrometer. Starting materials of oximes were prepared according to previously reported methods.[15]

General Procedure for Thiazole Products 3. Oxime **1** (0.5 mmol), anhydride **2** (1.5 mmol), CuI (10 mol%), KSCN (1.0 mmol), in toluene (3 mL) were added to a 25 mL Schlenk tube with magnetic stirrer bar. The mixture was stirred at 120 °C (oil bath temperature) for 24 h under N_2. After the reaction was finished (monitored by TLC), the mixture was cooled to room temperature. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified by column chromatography EtOAc/hexanes (1:20) on silica gel.

General Procedure for Naphtho[1,2-*d*]thiazole Products 4. Oxime **1** (0.5 mmol), anhydride (1.5 mmol), CuI (10 mol%), KSCN (1.0 mmol), in toluene (3 mL) were added to a 25 mL Schlenk tube with magnetic stirrer bar. The mixture was stirred at 120 °C (oil bath temperature) for 24 h under N_2. After the reaction was finished (monitored by TLC), the mixture was cooled to room temperature. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The crude products were dissolved in toluene (2 mL) with DDQ (0.6 mmol) and added to a 25 mL Schlenk tube with magnetic stirrer bar. The mixture was stirred at 120 °C (oil bath temperature) for 10 h under N_2. After the reaction was finished (monitored by GC-MS), the mixture was cooled to room temperature. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. Finally, it was purified by column chromatography EtOAc/hexanes (1:20) on silica gel.

*2-Methyl-4-phenylthiazole (**3a**).*[16] Red solid (64 mg, 73%), mp =64−65 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.88 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 6.9 Hz, 2H), 7.36−7.29 (m, 2H), 2.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 155.1, 134.5, 128.7, 127.9, 126.3, 112.2, 19.3. MS (EI, 70 eV) m/z: 175 (M^+), 134, 108, 89, 77. IR (KBr) ν (cm^{-1}): 2924, 1500, 1375, 1171, 1027, 731.

*2-Methyl-4-(p-tolyl)thiazole (**3b**).*[16] Brown oil (59 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1 Hz, 2H), 7.24 (s, 1H), 7.22 (d, J = 7.9 Hz, 2H), 2.77 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 155.2, 137.8, 131.8, 129.4, 126.2, 111.4, 21.2, 19.3. MS (EI, 70 eV) m/z: 189 (M^+), 148, 115, 91, 77. IR (KBr) ν (cm^{-1}): 2924, 1503, 1265, 1172, 832, 744.

*4-([1,1′-Biphenyl]-4-yl)-2-methylthiazole (**3c**).* Red solid (68 mg, 54%), mp =108−109 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.96 (d, J = 8.3 Hz, 2H), 7.67−7.62 (m, 4H), 7.47−7.43 (m, 2H), 7.39−7.32 (m, 2H), 2.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 154.8, 140.7, 133.6, 128.8, 127.4, 127.4, 127.0, 126.7, 112.3, 19.4. MS (EI, 70 eV) m/z: 251 (M^+), 210, 165, 152, 104, 91. IR (KBr) ν (cm^{-1}): 2925, 1602, 1406, 1169, 848, 743, 692. HRMS-ESI (m/z): calcd for $C_{16}H_{14}NS$, $[M+H]^+$: 252.0841; found, 252.0845.

*4-(4-Fluorophenyl)-2-methylthiazole (**3d**).* Brown oil (63 mg, 65%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.81 (m, 2H), 7.23 (s, 1H), 7.13−7.06 (m, 2H), 2.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 162.6 (d, J = 246 Hz), 154.1, 130.8 (d, J = 3 Hz), 128.0 (d, J = 8 Hz), 115.6 (d, J = 22 Hz), 111.8, 19.3. MS (EI, 70 eV) m/z: 193 (M^+), 152, 132, 107, 76. IR (KBr) ν (cm^{-1}): 2926, 1600, 1505, 1167, 847, 745. HRMS-ESI (m/z): calcd for $C_{10}H_9FNS$, $[M+H]^+$:194.0434; found, 194.0432.

*4-(4-Chlorophenyl)-2-methylthiazole (**3e**).*[16] Red solid (67 mg, 64%), mp =121−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.29 (s, 1H), 2.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 154.0, 133.7, 133.0, 128.9, 127.6, 112.6, 19.3. MS (EI, 70 eV) m/z: 209 (M^+), 168, 133, 104, 89. IR (KBr) ν (cm^{-1}): 2924, 1506, 1402, 850, 826, 744.

*4-(4-Bromophenyl)-2-methylthiazole (**3f**).*[17] Yellow solid (79 mg, 62%), mp =132−133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.30 (s, 1H), 2.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 153.9, 133.4, 131.8, 127.9, 122.0, 112.7, 19.3. MS (EI, 70 eV) m/z: 255 (M^+), 211, 133, 89, 75. IR (KBr) ν (cm^{-1}): 1638, 1505, 1170, 825, 743.

*4-(4-Iodophenyl)-2-methylthiazole (**3g**).* White solid (80 mg, 53%), mp =141−143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.31 (s, 1H), 2.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 154.0, 137.8, 134.0, 128.1, 112.3, 93.6, 19.3. MS (EI, 70 eV) m/z: 301 (M^+), 260, 133, 89, 74. IR (KBr) ν (cm^{-1}): 2923, 1504, 1170, 848, 743. HRMS-ESI (m/z): calcd for $C_{10}H_9INS$, $[M+H]^+$: 301.9495; found, 301.9490.

*4-(4-Methoxyphenyl)-2-methylthiazole (**3h**).*[16] Yellow solid (84 mg, 82%), mp =71−73 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.6 Hz, 2H)„ 7.16 (s, 1H), 6.94 (d, J = 8.6 Hz, 2H), 3.83 (s, 3H), 2.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 159.5, 154.9, 127.6, 127.5, 114.1, 110.5, 55.3, 19.3. MS (EI, 70 eV) m/z: 205 (M^+), 190, 164, 149, 121, 77. IR (KBr) ν (cm^{-1}): 2934, 1505, 1279, 1174, 1032, 835, 749.

*4-(4-(Benzyloxy)phenyl)-2-methylthiazole (**3i**).* White solid (118 mg, 84%), mp =105−106 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.37−7.30 (m, 1H), 7.17 (s, 1H), 7.02 (d, J = 8.6 Hz, 2H), 5.11 (s, 2H), 2.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 158.7, 154.9, 136.9, 128.6, 128.0, 127.8, 127.6, 127.5, 115.1, 110.6, 70.1, 19.3. MS (EI, 70 eV) m/z: 281 (M^+), 190, 162, 121, 91, 65. IR (KBr) ν (cm^{-1}): 2920, 1607, 1248, 1172, 1013, 833, 745. HRMS-ESI (m/z): calcd for $C_{17}H_{16}NOS$, $[M+H]^+$: 282.0947; found, 282.0945.

*Methyl 4-(2-Methylthiazol-4-yl)benzoate (**3j**).* White solid (62 mg, 53%), mp =112−113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.3 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 7.43 (s, 1H), 3.92 (s, 3H), 2.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 166.3, 154.0, 138.6, 130.1, 129.3, 126.1, 114.3, 52.1, 19.3. MS (EI, 70 eV) m/z: 233 (M^+), 202, 161, 133, 89, 66. IR (KBr) ν (cm^{-1}): 1715, 1608, 1278, 856, 747. HRMS-ESI (m/z): calcd for $C_{12}H_{12}NO_2S$, $[M+H]^+$: 234.0583; found, 234.0583.

*2-Methyl-4-(4-nitrophenyl)thiazole (**3k**).*[18] Red solid (57 mg, 52%), mp =133−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.6 Hz, 2H), 8.03 (d, J = 8.6 Hz, 2H), 7.52 (s, 1H), 2.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 152.7, 147.2, 140.3, 126.8, 124.2, 115.9, 19.3. MS (EI, 70 eV) m/z: 220 (M^+), 190, 174, 149, 89, 77. IR (KBr) ν (cm^{-1}): 2925, 1597, 1502, 1339, 1170, 849, 746.

*4-(2-Methoxyphenyl)-2-methylthiazole (**3l**).* Yellow oil (67 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.7 Hz, 1H), 7.72 (s, 1H), 7.28−7.23 (m, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 3.90 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 156.7, 150.7, 130.1, 128.7, 123.4, 120.9, 116.6, 111.1, 55.4, 19.2. MS (EI, 70 eV) m/z: 205 (M^+), 190, 164, 131, 91, 77. IR (KBr) ν (cm^{-1}): 2931, 1511, 1478, 1243, 1171, 1024, 756, 639. HRMS-ESI (m/z): calcd for $C_{11}H_{12}NOS$, $[M+H]^+$: 206.0634; found, 206.0635.

*4-(3-Methoxyphenyl)-2-methylthiazole (**3m**).* Red oil (74 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.1 Hz, 2H), 7.35−7.28 (m, 2H), 6.88 (d, J = 7.7 Hz, 1H), 3.87 (s, 3H), 2.77 (s, 3H). ^{13}C

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NMR (100 MHz, $CDCl_3$) δ 165.8, 160.0, 155.0, 135.9, 129.7, 118.8, 114.0, 112.6, 111.7, 55.4, 19.3. MS (EI, 70 eV) m/z: 205 (M^+), 175, 134, 121, 91, 77. IR (KBr) ν (cm^{-1}): 2929, 1605, 1521, 1244, 1043, 792, 744. HRMS-ESI (m/z): calcd for $C_{11}H_{12}NOS$, $[M+H]^+$: 206.0634; found, 206.0633.

*4-(3,4-Dimethylphenyl)-2-methylthiazole (**3n**).* Red oil (67 mg, 66%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.25 (s, 1H), 7.17 (d, J = 7.8 Hz, 1H), 2.78 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 155.3, 136.9, 136.5, 132.2, 139.0, 127.6, 123.7, 111.4, 19.8, 19.6, 19.3. MS (EI, 70 eV) m/z: 203 (M^+), 162, 147, 128, 115, 77. IR (KBr) ν (cm^{-1}): 2920, 1501, 1378, 1178, 815, 743. HRMS-ESI (m/z): calcd for $C_{12}H_{14}NS$, $[M+H]^+$: 204.0841; found, 204.0841.

*4-(Benzo[d][1,3]dioxol-5-yl)-2-methylthiazole (**3o**).* White solid (85 mg, 78%), mp =90−91 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.1 Hz, 1H), 7.34 (s, 1H), 7.13 (s, 1H), 6.84 (d, J = 8.1 Hz, 1H), 5.97 (s, 2H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 154.8, 148.0, 147.5, 129.0, 120.2, 111.0, 108.5, 106.9, 101.2, 19.3. MS (EI, 70 eV) m/z: 219 (M^+), 178, 148, 120, 94. IR (KBr) ν (cm^{-1}): 2896, 1520, 1286, 1240, 1040, 931, 741. HRMS-ESI (m/z): calcd for $C_{11}H_{10}NO_2S$, $[M+H]^+$: 220.0427; found, 220.0426.

*2-Methyl-4-(naphthalen-1-yl)thiazole (**3p**).* Brown oil (96 mg, 85%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.30−8.23 (m, 1H), 7.91−7.88 (m, 2H), 7.68 (d, J = 7.0 Hz, 1H), 7.54−7.50 (m, 3H), 7.28 (s, 1H), 2.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 154.6, 133.8, 132.8, 131.5, 128.7, 128.2, 127.4, 126.3, 125.8, 125.8, 125.2, 116.3, 19.3. MS (EI, 70 eV) m/z: 225 (M^+), 184, 152, 139, 92, 79. IR (KBr) ν (cm^{-1}): 2923, 1508, 1183, 1161, 805, 778. HRMS-ESI (m/z): calcd for $C_{14}H_{12}NS$, $[M+H]^+$: 226.0685; found, 226.0688.

*2-Methyl-4-(thiophen-2-yl)thiazole (**3q**).* Brown oil (49 mg, 54%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 2.4 Hz, 1H), 7.28 (d, J = 4.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.07 (t, J = 4.3 Hz, 1H), 2.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 149.5, 138.4, 127.7, 125.0, 123.9, 111.0, 19.2. MS (EI, 70 eV) m/z: 181 (M^+), 140, 96, 82, 68. IR (KBr) ν (cm^{-1}): 3106, 2923, 1549, 1164, 804, 735, 699. HRMS-ESI (m/z): calcd for $C_8H_8NS_2$, $[M+H]^+$: 182.0093; found, 182.0089.

*2,5-Dimethyl-4-phenylthiazole (**3r**).*[19] Yellow oil (48 mg, 51%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.3 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 2.69 (s, 3H), 2.51 (s,3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 150.4, 134.9, 128.6, 128.4, 127.5, 19.0, 12.5. MS (EI, 70 eV) m/z: 189 (M^+), 175, 147, 132, 104, 77. IR (KBr) ν (cm^{-1}): 2924, 1504, 1442, 1189, 771, 700.

*4-Butyl-2-methyl-5-propylthiazole (**3s**).* Yellow oil (47 mg, 48%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.70−2.56 (m, 7H), 1.65−1.58 (m, 4H), 1.40−1.33 (m, 2H), 0.97−0.90 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 151.6, 131.4, 32.1, 28.9, 28.2, 25.3, 22.6, 19.0, 13.9, 13.7. MS (EI, 70 eV) m/z: 197 (M^+), 182, 155, 127, 85, 79. IR (KBr) ν (cm^{-1}): 2927, 2858, 1459, 1184, 801. HRMS-ESI (m/z): calcd for $C_{11}H_{20}NS$, $[M+H]^+$: 198.1311; found, 198.1314.

*2-Methyl-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazole (**3t**).* Yellow oil (47 mg, 56%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.96−2.86 (m, 2H), 2.81−2.71 (m, 2H), 2.57 (s, 3H), 1.83−1.82 (m, 2H), 1.75−1.66 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 154.5, 131.8, 31.7, 31.5, 28.0, 26.6, 26.3, 18.7. MS (EI, 70 eV) m/z: 167 (M^+), 126, 111, 93, 91, 77. IR (KBr) ν (cm^{-1}): 2923, 2853, 1653, 1089,802, 684. HRMS-ESI (m/z): calcd for $C_9H_{14}NS$, $[M+H]^+$: 168.0841; found, 168.0835.

*2-Methyl-4,5,6,7,8,9-hexahydrocycloocta[d]thiazole (**3u**).* Yellow oil (48 mg, 53%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.81−2.80 (m, 4H), 2.61 (s, 3H), 1.71−1.66 (m, 4H), 1.41 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 152.4, 130.4, 31.4, 29.7, 28.1, 26.0, 25.5, 24.5, 19.0. MS (EI, 70 eV) m/z: 181 (M^+), 153, 140, 125, 107, 79. IR (KBr) ν (cm^{-1}): 2922, 2852, 1459, 958, 801. HRMS-ESI (m/z): calcd for $C_{10}H_{16}NS$, $[M+H]^+$: 182.0998; found, 182.1000.

*2-Ethyl-4-phenylthiazole (**3v**).* Red oil (68 mg, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.2 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.35−7.30 (m, 2H), 3.11 (q, J = 7.6 Hz, 2H), 1.45 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 155.0, 134.7, 128.7, 127.9, 126.4, 111.8, 27.1, 14.3. MS (EI, 70 eV) m/z: 189 (M^+), 174, 134, 108, 89, 77. IR (KBr) ν (cm^{-1}): 2928, 1499, 1378, 1031, 731, 692. HRMS-ESI (m/z): calcd for $C_{11}H_{12}NS$, $[M+H]^+$: 190.0685; found, 190.0683.

*4-Phenyl-2-propylthiazole (**3w**).* Red oil (64 mg, 63%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.9 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.36−7.30 (m, 2H), 3.05 (t, J = 7.6 Hz, 2H), 1.96−1.83 (m, 2H), 1.07 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 155.0, 134.7, 128.7, 127.9, 126.4, 111.9, 35.6, 23.5, 13.7. MS (EI, 70 eV) m/z: 203 (M^+), 188, 175, 134, 89, 77. IR (KBr) ν (cm^{-1}): 2928, 1498, 1444, 1168, 1022, 730, 692. HRMS-ESI (m/z): calcd for $C_{12}H_{14}NS$, $[M+H]^+$: 204.0841; found, 204.0839.

*2-Isopropyl-4-phenylthiazole (**3x**).* Yellow oil (74 mg, 73%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.4 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.35−7.29 (m, 2H), 3.55−3.23 (m, 1H), 1.47 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 154.7, 134.7, 128.7, 128.0, 126.4, 111.4, 33.4, 23.3. MS (EI, 70 eV) m/z: 203 (M^+), 188, 134, 108, 89, 77. IR (KBr) ν (cm^{-1}): 2927, 1602, 1445, 1070, 843, 774. HRMS-ESI (m/z): calcd for $C_{12}H_{14}NS$, $[M+H]^+$: 204.0841; found, 204.0839.

*2-(tert-Butyl)-4-phenylthiazole (**3y**).* Yellow oil (80 mg, 74%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.35−7.28 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 154.7, 135.0, 128.6, 127.8, 126.4, 111.4, 37.8, 31.0. MS (EI, 70 eV) m/z: 217 (M^+), 202, 175, 134, 102, 89. IR (KBr) ν (cm^{-1}): 2963, 1494, 1364, 1069, 731, 692. HRMS-ESI (m/z): calcd for $C_{13}H_{16}NS$, $[M+H]^+$: 218.0998; found, 218.1000.

*2-Cyclohexyl-4-phenylthiazole (**3z**).* Red oil (95 mg, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.4 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.36−7.30 (m, 2H), 3.15−3.00 (m, 1H), 2.23−2.20 (m, 2H), 1.90−1.87(m, 2H), 1.78−1.75 (m, 1H), 1.63−1.55 (m, 2H), 1.47−1.41 (m, 2H), 1.36−1.28 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 154.7, 134.9, 128.7, 127.9, 126.4, 111.3, 42.8, 33.9, 26.1, 25.9. MS (EI, 70 eV) m/z: 243 (M^+), 188, 175, 134, 89, 77. IR (KBr) ν (cm^{-1}): 2957, 2853, 1494, 1447, 1184, 730, 691. HRMS-ESI (m/z): calcd for $C_{15}H_{18}NS$, $[M+H]^+$: 244.1154; found, 244.1156.

*2-Methylnaphtho[1,2-d]thiazole (**4a**).* Yellow solid (58 mg, 58%), mp =94−95 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.70−7.64 (m, 1H), 7.61−7.54 (m, 1H), 2.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 149.4, 131.9, 131.8, 128.3, 128.0, 126.8, 125.9, 125.3, 123.7, 118.8, 20.1. MS (EI, 70 eV) m/z: 199 (M^+), 158, 114, 79, 63. IR (KBr) ν (cm^{-1}): 2923, 2852, 1514, 1166, 804, 744. HRMS-ESI (m/z): calcd for $C_{12}H_{10}NS$, $[M+H]^+$: 200.0528; found, 200.0528.

*7-Methoxy-2-methylnaphtho[1,2-d]thiazole (**4b**).* Red oil (62 mg, 54%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 9.0 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.31−7.28 (m, 1H), 7.25 (s, 1H), 3.94 (s, 3H), 2.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 157.8, 149.7, 133.3, 129. 8, 125.4, 124.4, 123.6, 119.4, 118.6, 107.0, 55.4, 20.1. IR (KBr) ν (cm^{-1}): 2922, 2850, 1625, 1248, 1169, 1029, 752. MS (EI, 70 eV) m/z: 229 (M^+), 214, 186, 145, 101, 69. HRMS-ESI (m/z): calcd for $C_{13}H_{12}NOS$, $[M+H]^+$: 230.0634; found, 230.0629.

*8-Methoxy-2-methylnaphtho[1,2-d]thiazole (**4c**).* Yellow oil (60 mg, 52%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 2.5 Hz, 1H), 7.82 (d, J = 8.9 Hz, 1H), 7.70 (s, 2H), 7.22−7.19 (m, 1H), 4.04 (s, 3H), 2.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.40, 158.7, 149.2, 132.5, 129.6, 129.6, 127.1, 125.1, 118.4, 116.3, 102.4, 55.6, 20.1. IR (KBr) ν (cm^{-1}): 2925, 2853, 1624, 1230, 1044, 831, 740.MS (EI, 70 eV) m/z: 229 (M^+), 214, 186, 145, 114, 101, 69. HRMS-ESI (m/z): calcd for $C_{13}H_{12}NOS$, $[M+H]^+$: 230.0634; found, 230.0633.

*8-Bromo-2-methylnaphtho[1,2-d]thiazole (**4d**).* Yellow solid (66 mg, 48%), mp =162−163 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 1.8 Hz, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.62 (dd, J = 8.7, 2.0 Hz, 1H), 2.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 148.5, 132.9, 130.3, 129.6, 129.3, 129.3, 126.3, 124.9, 121.1, 119.3, 20.1. MS (EI, 70 eV) m/z: 277 (M^+), 198, 154, 113, 98, 78. IR (KBr) ν (cm^{-1}): 2922, 2853, 1644, 1263, 825, 756.HRMS-ESI (m/z): calcd for $C_{12}H_9BrNS$, $[M+H]^+$: 277.9634; found, 277.9631.

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■ ASSOCIATED CONTENT

Supporting Information

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^{1}H and ^{13}C NMR spectra for all compounds prepared (PDF)

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Notes

The authors declare no competing financial interest.

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