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Article

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Copper(I)-Catalyzed Tandem One-Pot Synthesis of 2-Arylthiobenzothiazoles and 2-Arylthiobenzoxazoles in Water

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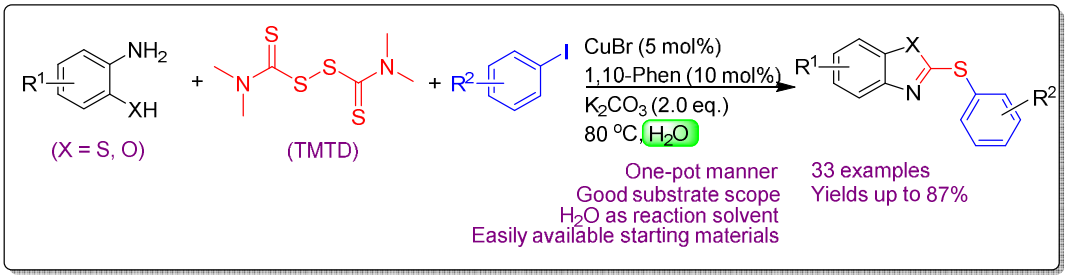


ABSTRACT

An efficient tandem process for the preparation of 2-arylthiobenzothiazoles has been developed. By condensation of 2-aminobenzenethiol with TMTD (tetramethylthiuram disulfide), 2-mercaptobenzothiazoles was *in-situ* generated, which susequently underwent coupling with iodobenzenes to give the desired 2-arylthiobenzothiazoles fluently in a one-pot manner. This method can also be used for the synthesis of 2-arylthiobenzoxazoles. Inexpensive metal catalyst and ligand, mild reaction temperature, and water as solvent make this protocol practically valuable and useful in organic synthesis.

INTRODUCTION

Heteroaromatic compounds possessing organothio groups and their derivatives are known to exhibit interesting biological activities.[1] These compounds possess potential application as anticancer, antimicrobial, antiviral, antitubercular, antihelmintic, antidiabetic, antifungal, and antibacterial agent.[2] Particularly, several 2-thio-substituted mercaptoazoles such as 2-arylthiobenzothiazoles have received much attention due to their unique structure and their uses as radioactive amyloid imagining agents,[3] and anticancer agents.[4] Some therapeutic agents containing this core structure have been reported, including avarol-3′-thiobenzothizole (A), PPAR receptor activator (B), cathepsin-D inhibitor (C) (Figure 1).[5] It is thus necessary to develop simple and eco-friendly synthetic methods for their preparations.

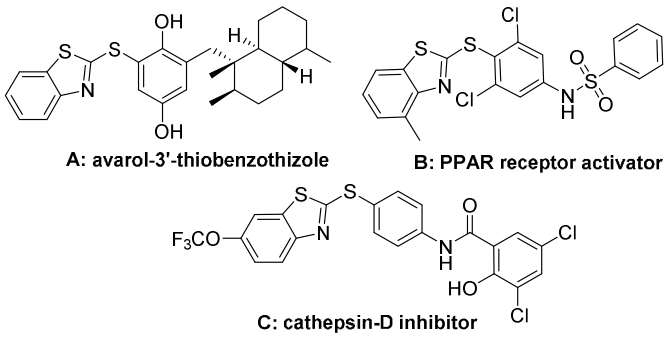


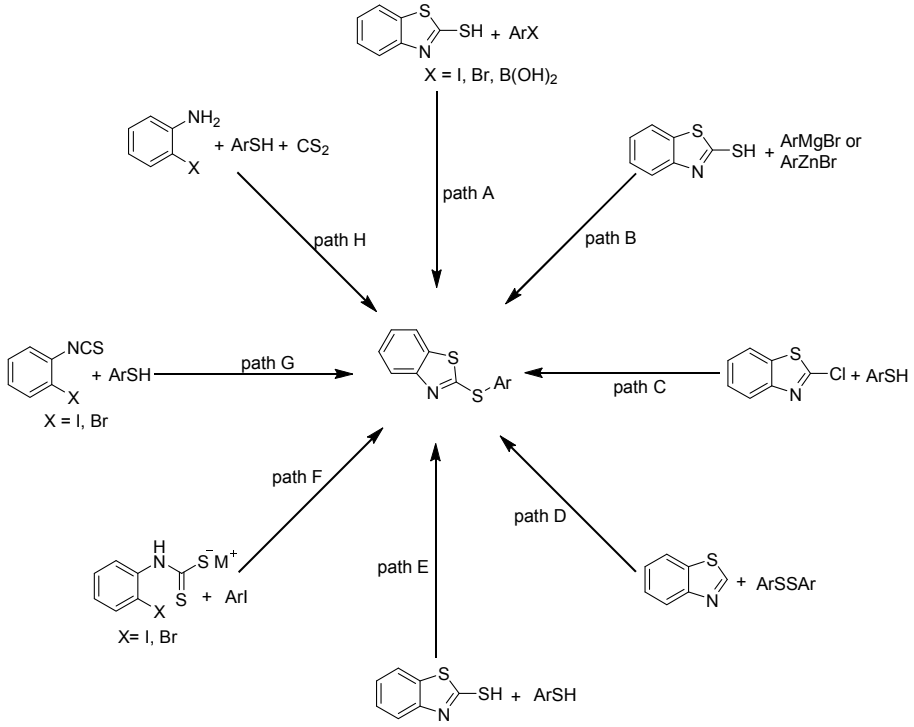
Figure 1. Representative Biologically Active 2-Arylthiobenzothiazoles.

Classically, 2-arylthiobenzothiazolesa are synthesized *via* the cross-coupling reactions of 2-mercaptobenzothiazoles with aryl halides (Scheme 1, path A),[6] or aryl boronic acids,[7] or Grignard reagents (Scheme 1, path B),[8] and the nucleophilic attack of arylthiols on preformed 2-halobenzothiazoles (Scheme 1, path C).[9] However, the preparation of 2-arylthiobenzothiazoles with these methods depends largely on the availability of the requisite, suitably substituted 2-halobenzothiazoles or 2-mercaptobenzothiazoles. Several other methods are available for the synthesis of

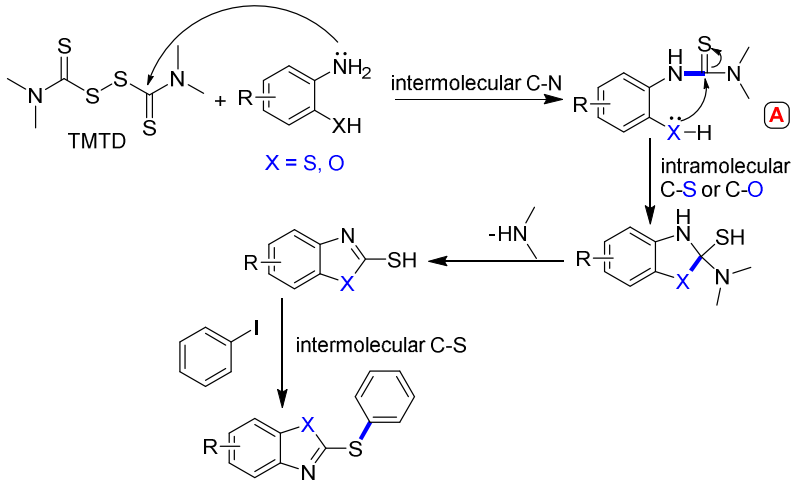
2-arylthiobenzothiazoles, including the *S*-arylation of benzothiazoles with diaryl disulfides (Scheme 1, path D)[10] or the direct functionalization of a heterocyclic C-H bond with aryl thiols in the presence of a copper reagent (Scheme 1, path E).[11] However, these copper-mediated reactions suffer from many drawbacks such as high reaction temperature, the usual requirement of stoichiometric copper salts. In recent years, one-pot, tandem, cascade or domino strategies, whereby multiple bonds can be constructed in a single reaction without the need to isolate the intermediates, are used to improve the efficiency of a chemical reaction.[12] Patel and co-workers reported Cu(I)-catalyzed sequential intra- and intermolecular C-S bond formation using dithiocarbamate salts (Scheme 1, path F)[13] and an efficient cascade process from 2-haloaryl isothiocyanates and S nucleophiles (Scheme 1, path G).[14] Ma and co-workers reported the synthesis of 2-thio-substituted benzothiazoles in good yields *via* a domino condensation (Scheme 1, path H).[15] Although significant progress has been achieved towards the synthesis of these compounds, the development of environmentally benign, facile, cheaper, and efficient *S*-arylation protocols is still desirable.

Thiuram reagents are cheap and commercially available organosulfur compounds with broad applications as fungicides, animal repellants, and vulcanization accelerators.[16] Because they are readily available and could be regarded as interesting reagents for the development of new synthetic transformations.[17] On the other hand, the development of environmentally friendly reaction medium, especially water, has been paid much attention.[18] Recently, we reported an efficient and practical method for the one-pot synthesis of 2-mercaptoazoles by using thiuram reagent (TMTD) in water.[19] For the continuous efforts on the study of benzoheterocycle compounds,[20] we wish to report here an efficient tandem protocol in water for the synthesis of

2-arylthiobenzothiazoles and 2-arylthiobenzoxazoles by using thiuram reagent (TMTD) (Scheme 2). In this one-pot arylation strategy, intermolecular C-N coupling of TMTD (tetramethylthiuram disulfide) would yield intermediate **A** (Scheme 2), which is then followed by an intramolecular C-S (or C-O) coupling, furnishing 2-mercaptobenzothiazole (or 2-mercaptobenzoxazole). Thus, the subsequent *in-situ* intermolecular C-S coupling between 2-mercaptobenzothiazole (or 2-mercaptobenzoxazole) and iodobenzene would generate 2-arylthiobenzothiazole (or 2-arylthiobenzoxazole) smoothly.



Scheme 1. Existing Synthesis Strategies towards 2-Arylthiobenzothiazoles.



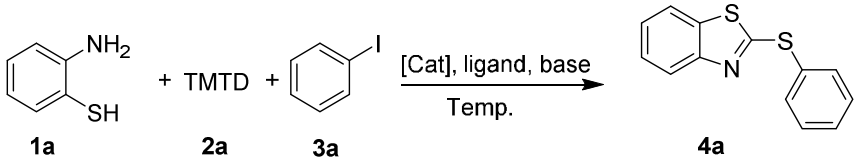
Scheme 2. Our Synthetic Strategy towards 2-Arylthiobenzothiazoles and 2-Arylthiobenzoxazoles.

RESULTS AND DISCUSSION

We selected 2-aminobenzenethio, TMTD (tetramethylthiuram disulfide) and iodobenzene as the starting material for the model reaction, and the screened reaction conditions are summarized in Table 1. The reaction took place to give the desired product **4a** in 20% yield under the conditions shown in entry 1 (10 mol% CuI, 10 mol% 1,10-phenanthroline, 2.0 equiv. of Na_2CO_3, 120 ^oC in H_2O). A slightly improved result was observed by changing H_2O to organic solvent DMF (entry 2). Since the first step of the three-component reaction is the condensation of 2-aminobenzenethiol with TMTD, we envisioned that changing the operational procedure might be helpful to increase the yield. Accordingly, 2-aminobenzenethiol was reacted with TMTD at 120 ^oC for 3 h and then CuI, iodobenzene, 1,10-phenanthroline, Na_2CO_3 were added before heating. This manipulation proved to be useful, providing the target molecular **4a** in 80% yield (entry 3). Encouraged by this result, various bases were investigated, and K_2CO_3 gave the best yield (entries 4-7). A number of other ligands were tested for this reaction (entries 8-10), and the results showed that other ligands displayed poor activity as compared with 1,10-phenanthroline. Subsequently, several copper catalysts

were investigated (entries 11-15), and CuBr was found to be the most effective catalyst for the current reaction (entry 11). Other metal catalysts, such as iron, nickel, or cobalt showed no catalytic activity (entries 16-18). 5 mol% of copper loading did not affect the yield of the product (entry 19), while the yield of the product was reduced to 48% when 5 mol% of 1,10-phenanthroline was used (entry 20). The screening of the base loading showed that 2.0 equiv. of K_2CO_3 was the optimal (entry 19 and entry 21). In addition, the yield dropped to 31% when the temperature was reduced to 60 ^oC (entries 22-24). Thus, the optimal reaction conditions were set and summarized in entry 23 (5 mol% of CuBr, 10 mol% of 1,10-phenanthroline, 2.0 equiv. of K_2CO_3 in water, heating at 80 ^oC).

Table 1. Reaction Conditions Screened for the Tandem Synthesis of 2-Arylthiobenzothiazole Starting from 2-Aminobenzenethiol, TMTD, and Iodobenzene[a]



1a **2a** **3a** **4a**

Entry	Catalyst	Base	Ligand	Temp. (^oC)	Yield (%)[b]
1	CuI	Na_2CO_3	1,10-phen	120	20
2	CuI	Na_2CO_3	1,10-phen	120	23[c]
3	CuI	Na_2CO_3	1,10-phen	120	80
4	CuI	K_3PO_4	1,10-phen	120	82
5	CuI	K_2CO_3	1,10-phen	120	83
6	CuI	KOH	1,10-phen	120	76

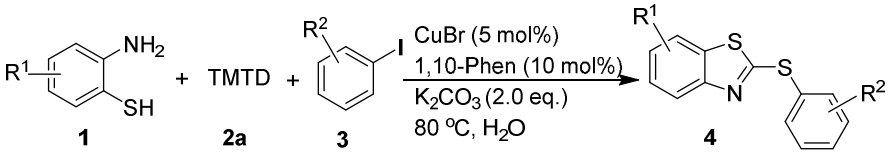
7	CuI	*t*-BuOK	1,10-phen	120	81
8	CuI	K_2CO_3	Bpy[d]	120	41
9	CuI	K_2CO_3	L-proline	120	trace
10	CuI	K_2CO_3	DMEDA[e]	120	trace
11	CuBr	K_2CO_3	1,10-phen	120	87
12	Cu_2O	K_2CO_3	1,10-phen	120	82
13	$CuCl_2{\cdot}2H_2O$	K_2CO_3	1,10-phen	120	84
14	$CuSO_4{\cdot}5H_2O$	K_2CO_3	1,10-phen	120	82
15	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	1,10-phen	120	80
16	$FeCl_3{\cdot}6H_2O$	K_2CO_3	1,10-phen	120	0
17	$NiCl_2{\cdot}6H_2O$	K_2CO_3	1,10-phen	120	0
18	$CoCl_2$	K_2CO_3	1,10-phen	120	0
19	CuBr (5%)	K_2CO_3	1,10-phen	120	87
20	CuBr (5%)	K_2CO_3	1,10-phen	120	48[f]
21	CuBr (5%)	K_2CO_3	1,10-phen	120	83[g]
22	CuBr (5%)	K_2CO_3	1,10-phen	100	87
23	**CuBr (5%)**	**K_2CO_3**	**1,10-phen**	**80**	**87**
24	CuBr (5%)	K_2CO_3	1,10-phen	60	31

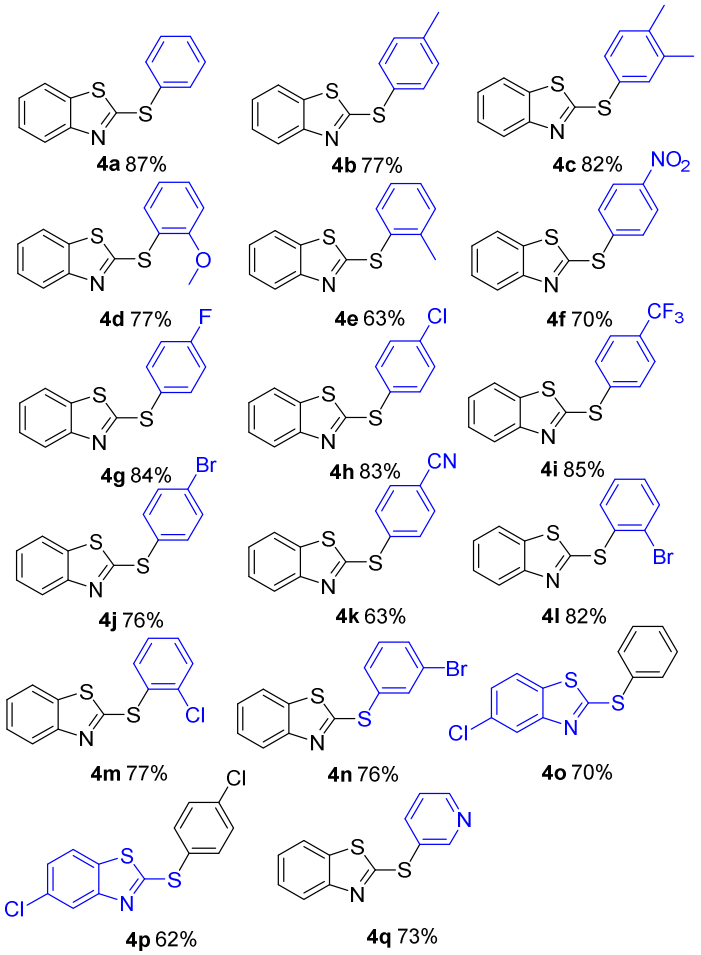
[a] Reaction conditions: **A** (for entries 1-2): **1a** (1.0 mmol), **2a** (0.6 mmol), **3a** (1.5 mmol), [Cat] (10 mol%), base (2.0 equiv.), ligand (10 mol%), H_2O (2 mL), 15 h, **B** (for entries 3-24): **1a** (1.0 mmol), **2a** (0.6 mmol), H_2O, 120 °C, 3 h; then **3a** (1.5 mmol), [Cat] (10 mol%), base (2.0 equiv.), ligand (10 mol%), 120-60 °C, 8 h. [b] Isolated yield. [c] DMF as solvent. [d] Bpy = 2,2'-Bipyridine, [e] DMEDA = *N,N*'-Dimethyl-1,2-ethanediamine, [f] Use of 5 mol% 1,10-phenanthroline. [g] Use of 1.5 equiv. of K_2CO_3.

By using the above optimized conditions, we explored the substrates scope and limitations of the three-component reaction (Table 2). Firstly, various aryl iodides were surveyed and proved to be applicable for this transformation, giving the

corresponding 2-arylthiobenzothiazoles successfully. For the electron-donating methyl or methoxy groups, generally good yields were obtained (**4b-4e**). Due to the possible steric hinderence, compound **4d** and **4e** were obtained in moderate yields (77% and 63%). Substrates bearing electron-withdrawing substituents also resulted in good yields. Halides such as F, Cl, and Br yielded the desired products in 76-84% yield (**4g**, **4h**, **4j**, **4m**, **4n**), while strong electron-withdrawing group (NO_2, CN) gave relatively low yields (**4f**, **4k**). Meanwhile, 2-amino-4-chlorobenzenethiol was also applicable for the transformation, giving the corresponding 2-arylthiobenzothiazoles in good yields (**4o**, **4p**). In addition, heterocyclic compound, such as 3-iodopyridine could also afford the corresponding products **4q** in good yield (73%), which showed the good substrate compatibility of this protocol.

Table 2. Formation of 2-Thiobenzothiazoles from 2-Aminobenzenethiols, TMTD and Iodobenzenes[a]

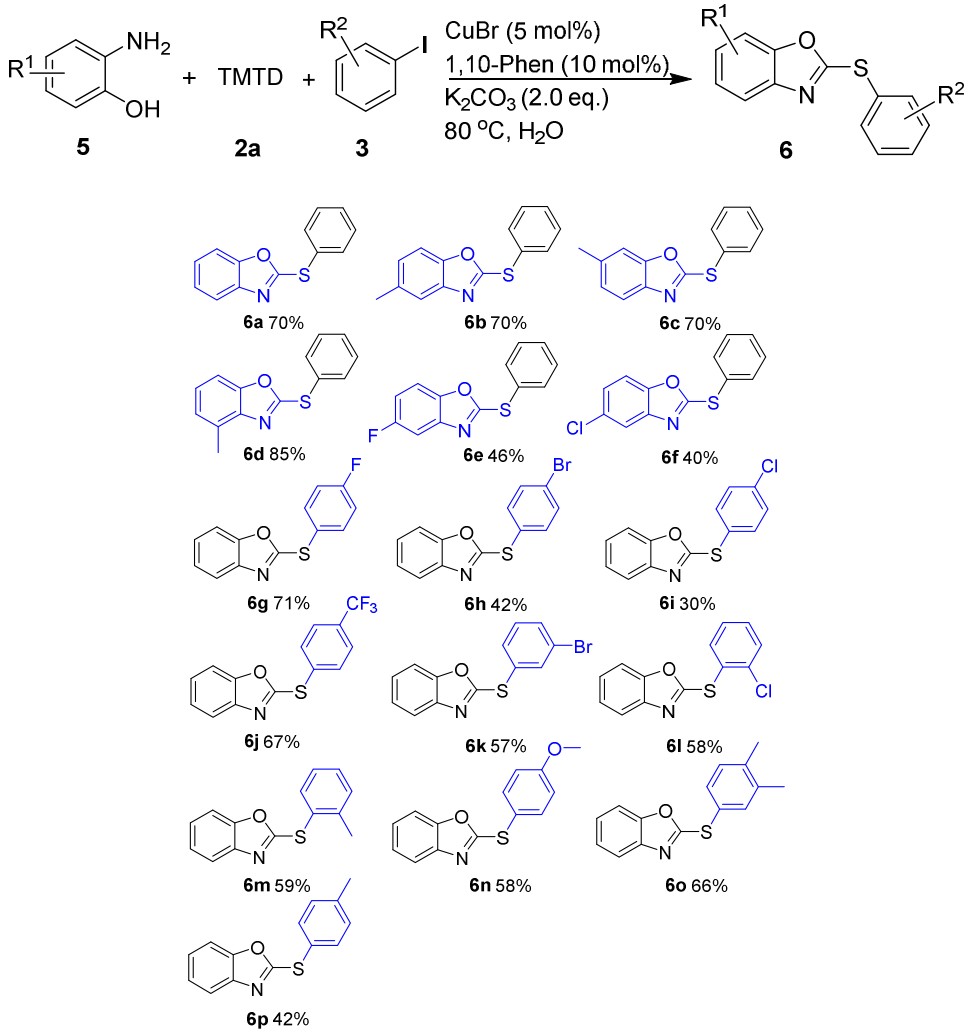




[a]Reaction conditions: **1** (1.0 mmol), **2a** (0.6 mmol), H_2O (2 mL), 120 °C, 3 h; then **3** (1.5 mmol), CuBr (5 mol%), 1,10-phenanthroline (10 mol%), K_2CO_3 (2.0 equiv.), 80 °C, 15 h. Isolated yield based on **1**.

Subsquently, 2-aminophenol was also tested in order to assess the versatility of the method (Table 3). It was found that both electron-deficient and electron-rich 2-aminophenol were applicable for this transformation, and the desired 2-arylthiobenzoxazoles **6a-6f** were obtained in moderate to good yields (40-85%). Similarly, we examined the reaction with a series of substituted iodobenzenes (**6g-6p**). Both electron-rich and electron-deficient aryl iodides were successfully transformed under the optimized conditions, furnishing the desired products in moderate to good yields (30-71%).

Table 3. Formation of 2-Thiobenzoxazoles from 2-Aminophenols, TMTD, and Iodobenzenes[a]



[a]Reaction conditions: **5** (1.0 mmol), **2a** (0.6 mmol), H_2O, 80 °C, 3 h; then **3** (1.5 mmol), CuBr (5 mol%), 1,10-phenanthroline (10 mol%), K_2CO_3 (2.0 equiv.), 80 °C, 15 h. Isolated yields based on **5**.

CONCLUSION

In summary, we have developed an efficient, operationally simple, and economically attractive copper-catalyzed tandem reaction for the synthesis of 2-Arylthiobenzothiazoles. 2-Arylthiobenzoxazole derivatives can also be obtained under the same reaction conditions. The protocol features inexpensive metal catalyst

and ligand, mild reaction temperature, broad substrates scope, and water as solvent, which makes it practically valuable and useful for the synthesis of some potential pharmaceutically active compounds.

EXPERIMENTAL SECTION

All starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. Yields refer to isolated compounds estimated to be >95% pure as determined by ^{1}H NMR and capillary GC analysis. NMR spectra were recorded on a Bruker AM400 NMR instrument in $CDCl_3$ using TMS as an internal standard. Chemical shifts are given in ppm and coupling constants (J) are given in Hz. All melting points were determined on a RY-1G melting point instrument without correction. High-resolution mass spectra (HRMS) were recorded on a Finnigan MAT 95Q or Finnigan 90 mass instrument (ESI). TLC was performed using aluminum plates coated with SiO_2 (Merck 60, F-254) and visualized with UV light at 254 nm. Column chromatography was performed on silica gel (200-300 mesh) with petroleum ether-EtOAc as eluent.

Typical procedure for reaction of 2-aminobenzenethiols with TMTD and iodobenzenes (TP1).

A mixture of 2-aminobenzenethiol (1.0 mmol) and TMTD (0.6 mmol) in H_2O (2.0 mL) was stirred at 120 ^{o}C for 3 h before CuBr (5 mol%), iodobenzene (1.5 mmol), 1,10-phenanthroline (10 mol%) and K_2CO_3 (2.0 equiv.) were added. The mixture was stirred at 80 ^{o}C and checked by TLC until the starting material was finished (about 15 h). The reaction was terminated with sat. NH_4Cl solution (3 mL) and then extracted with ethyl acetate. The crude solution was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography

to afford the desired product **4a**.

Typical procedure for reaction of 2-aminophenols with TMTD and iodobenzenes (TP2).

A mixture of 2-aminophenol (1.0 mmol) and TMTD (0.6 mmol) in H_2O (2.0 mL) was stirred at 80 ^oC for 3 h before CuBr (5 mol%), iodobenzene (1.5 mmol) 1,10-phenanthroline (10 mol%) and K_2CO_3 (2.0 equiv.) were added. The mixture was stirred at 80 ^oC and checked by TLC until the starting material was finished (about 15 h). The reaction was terminated with sat. NH_4Cl solution (3 mL) and then extracted with ethyl acetate. The crude solution was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography to afford the desired product **6a**.

Experiment data

2-(Phenylthio)benzo[*d*]thiazole (4a)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4a** as a yellow oil (211 mg, yield = 87%). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.85 (d, 1H, J = 8.0 Hz), 7.66 (d, 2H, J = 8.0 Hz), 7.55 (d, 1H, J = 8.0 Hz), 7.43-7.30 (m, 4H), 7.17 (t, 1H, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 169.4, 153.8, 135.4, 135.2, 130.3, 129.8, 129.8, 126.0, 124.2, 121.8, 120.7. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{13}H_{10}NS_2$ (244.0249), found: 244.0257.

2-(*p*-Tolylthio)benzo[*d*]thiazole (4b)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4b** as a yellow oil (198 mg, yield = 77%). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.75 (d, 1H, J = 8.0 Hz), 7.49 (d, 3H, J = 8.0 Hz), 7.26 (t, 1H, J = 8.0 Hz), 7.16-7.09 (m, 3H), 2.30 (s,

3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 169.8, 153.0, 140.1, 134.5, 134.4, 129.7, 125.1, 125.1, 123.1, 120.7, 119.7, 20.4. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{12}NS_2$ (258.0406), found: 258.0412.

2-((3,4-Dimethylphenyl)thio)benzo[*d*]thiazole (4c)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4c** as a colorless oil (222 mg, yield = 82%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.82 (d, 1H, *J* = 8.0 Hz), 7.50-7.27 (m, 4H), 7.13 (t, 2H, *J* = 8.0 Hz), 2.22 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 170.9, 154.1, 139.8, 138.6, 136.4, 135.5, 133.0, 131.2, 126.3, 126.1, 124.1, 121.8, 120.8, 19.8, 19.7. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{15}H_{14}NS_2$ (272.0562), found: 272.0552.

2-((2-Methoxyphenyl)thio)benzo[*d*]thiazole (4d)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4d** as a colorless oil (210 mg, yield = 77%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.88 (d, 1H, *J* = 8.0 Hz), 7.68 (d, 1H, *J* = 8.0 Hz), 7.61 (d, 1H, *J* = 8.0 Hz), 7.48 (t, 1H, *J* = 8.0 Hz), 7.37 (t, 1H, *J* = 8.0 Hz), 7.22 (t, 1H, *J* = 8.0 Hz), 7.04-6.97 (m, 2H), 3.80 (d, 3H, *J* = 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 169.9, 159.9, 154.1, 137.4, 135.6, 132.8, 126.0, 124.1, 121.7, 121.5, 120.8, 117.6, 112.0, 56.0. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{12}NOS_2$ (274.0355), found: 274.0362.

2-(*o*-Tolylthio)benzo[*d*]thiazole (4e)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4e** as a colorless oil (162 mg, yield = 63%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.84 (d, 1H, *J* = 8.0 Hz), 7.68 (d, 1H, *J* = 8.0 Hz), 7.56 (d, 1H, *J* = 8.0 Hz), 7.41-7.32 (m, 3H),

7.26-7.17 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 169.9, 154.2, 143.2, 137.1, 135.5, 131.5, 131.3, 129.1, 127.5, 126.1, 124.2, 121.8, 120.8, 20.9. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{12}NS_2$ (258.0406), found: 258.0412.

2-((4-Nitrophenyl)thio)benzo[*d*]thiazole (4f)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4f** as a white solid (202 mg, yield = 70%). m.p.: 77-79 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 8.09 (d, 2H, *J* = 8.0 Hz), 7.83 (d, 1H, *J* = 8.0 Hz), 7.64 (d, 3H, *J* = 8.0 Hz), 7.34 (t, 1H, *J* = 8.0 Hz), 7.24 (t, 1H, *J* = 8.0 Hz), ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 162.0, 152.5, 146.9, 139.0, 135.3, 131.8, 125.8, 124.7, 123.6, 121.9, 120.3. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9N_2O_2S_2$ (289.0100), found: 289.0108.

2-((4-Fluorophenyl)thio)benzo[*d*]thiazole (4g)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4g** as a colorless oil (220 mg, yield = 84%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.86 (d, 1H, *J* = 8.0 Hz), 7.72-7.69 (m, 2H), 7.64 (d, 1H, *J* = 8.0 Hz), 7.39 (t, 1H, *J* = 8.0 Hz), 7.25 (t, 1H, *J* = 8.0 Hz), 7.15 (t, 2H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 169.6, 164.3 (d, *J* = 250 Hz), 154.1, 137.9 ( ), 135.6, 126.4, 125.3 (d, *J* = 4.0 Hz), 124.5, 122.1, 121.0, 117.4 (d, *J* = 22 Hz). HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9FNS_2$ (262.0155), found: 262.0146.

2-((4-Chlorophenyl)thio)benzo[*d*]thiazole (4h)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4h** as a colorless oil (230 mg, yield = 83%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.86 (d, 1H, *J* = 8.0 Hz), 7.60 (t, 3H, *J* = 8.0 Hz), 7.36 (t, 3H, *J* = 8.0 Hz), 7.23 (t, 1H, *J* = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 168.1, 153.6, 136.7, 136.2, 135.4, 130.0, 128.2, 126.1, 124.4, 121.9, 120.7. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9ClNS_2$ (277.9860), found: 277.9865.

2-((4-(Trifluoromethyl)phenyl)thio)benzo[*d*]thiazole (4i)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4i** as a colorless oil (264 mg, yield = 85%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.89 (d, 1H, *J* = 8.0 Hz), 7.74 (d, 2H, *J* = 8.0 Hz), 7.64 (t, 3H, *J* = 8.0 Hz), 7.38 (t, 1H, *J* = 8.0 Hz), 7.26 (t, 1H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 165.8, 153.7, 136.0, 135.4, 134.2, 131.8 (q, *J* = 33 Hz), 126.7 (q, *J* = 4.0 Hz), 126.6, 125.2, 123.8 (q, *J* = 258 Hz), 121.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_9F_3NS_2$ (312.0123), found: 312.0117.

2-((4-Bromophenyl)thio)benzo[*d*]thiazole (4j)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4j** as a colorless oil (244 mg, yield = 76%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.85 (d, 1H, *J* = 8.0 Hz), 7.60 (d, 1H, *J* = 8.0 Hz), 7.53-7.48 (m, 4H), 7.35 (t, 1H, *J* = 8.0 Hz), 7.22 (t, 1H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 167.8, 153.6, 136.3, 135.4, 132.9, 128.9, 126.2, 125.0, 124.4, 121.9, 120.7. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9BrNS_2$ (321.9355), found: 321.9347.

4-(Benzo[*d*]thiazol-2-ylthio)benzonitrile (4k)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4k** as a white solid (169 mg, yield = 63%). m.p.:94-96 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.82 (d, 1H, *J* = 8.0 Hz), 7.64-7.53 (m, 5H), 7.34 (t, 1H, *J* = 8.0 Hz), 7.24 (t, 1H, *J* =

8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 162.6, 152.4, 136.4, 135.0, 132.1, 131.9, 125.5, 124.3, 121.6, 120.1, 117.0, 111.8. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_9N_2S_2$ (269.0203), found: 269.0211.

2-((2-Bromophenyl)thio)benzo[*d*]thiazole (4l)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4l** as a colorless oil (263 mg, yield = 82%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.91 (d, 1H, *J* = 8.0 Hz), 7.79-7.65 (m, 3H), 7.42-7.25 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 166.8, 153.7, 136.7, 135.7, 134.0, 131.6, 131.6, 129.5, 128.5, 126.1, 124.5, 122.1, 120.8. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9BrNS_2$ (321.9355), found: 321.9361.

2-((2-Chlorophenyl)thio)benzo[*d*]thiazole (4m)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4m** as a colorless oil (213 mg, yield = 77%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.89 (d, 1H, *J* = 8.0 Hz), 7.75 (d, 1H, *J* = 8.0 Hz), 7.64 (d, 1H, *J* = 8.0 Hz), 7.53 (d, 1H, *J* = 8.0 Hz), 7.41-7.36 (m, 2H), 7.32-7.23 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 166.7, 153.7, 138.8, 136.9, 135.6, 131.6, 130.6, 129.4, 127.8, 126.1, 124.5, 122.0, 120.8. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9ClNS_2$ (277.9860), found: 277.9855.

2-((3-Bromophenyl)thio)benzo[*d*]thiazole (4n)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4n** as a colorless oil (244 mg, yield = 76%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.89-7.84 (m, 2H), 7.65-7.55 (m, 3H), 7.38 (t, 1H, *J* = 8.0 Hz), 7.29-7.23 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 167.2, 153.6, 137.0, 135.5, 133.2, 133.1, 132.0, 131.0,

126.2, 124.6, 123.1, 122.1, 120.8. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9BrNS_2$ (321.9355), found: 321.9362.

5-Chloro-2-(phenylthio)benzo[*d*]thiazole (4o)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4o** as a white solid (194 mg, yield = 70%). m.p.: 72-74 ^oC. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.67 (d, 1H, *J* = 4.0 Hz), 7.58-7.55 (m, 2H), 7.39-7.30 (m, 4H), 7.05-7.02 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 171.2, 153.7, 134.4, 132.6, 131.0, 129.7, 129.0, 128.3, 123.5, 120.6, 120.4. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9ClNS_2$ (277.9860), found: 277.9866.

5-Chloro-2-((4-chlorophenyl)thio)benzo[*d*]thiazole (4p)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4p** as a white solid (193 mg, yield = 62%). M.p.: 118-120 ^oC. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.76 (d, 1H, *J* = 4.0 Hz), 7.57 (d, 2H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 8.0 Hz), 7.37 (d, 2H, *J* = 8.0 Hz), 7.18-7.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 169.8, 153.6, 136.2, 135.6, 132.6, 131.3, 129.2, 126.8, 123.8, 120.8, 120.4. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_8Cl_2NS_2$ (311.9470), found: 311.9476.

2-(Pyridin-3-ylthio)benzo[*d*]thiazole (4q)

According to **TP1**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **4q** as a brown solid (178 mg, yield = 73%). m.p.: 76-78 ^oC. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 8.74 (s, 1H), 8.52 (s, 1H), 7.84 (d, 1H, *J* = 8.0 Hz), 7.70 (d, 1H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 8.0 Hz), 7.24-7.10 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 165.6, 153.5, 152.4, 149.8, 141.3, 134.4, 126.4, 125.3, 123.6, 123.4, 121.0,

119.8. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{12}H_9N_2S_2$ (245.0202), found: 245.0211.

2-(Phenylthio)benzo[*d*]oxazole (6a)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6a** as a yellow oil (159 mg, yield = 70%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.69-7.67 (m, 2H), 7.59-7.57 (m, 1H), 7.44-7.36 (m, 4H), 7.26-7.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 163.2, 151.7, 141.8, 134.3, 129.7, 129.5, 127.0, 124.2, 124.2, 118.9, 109.9. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_{10}NOS$ (228.0478), found: 228.0472.

5-Methyl-2-(phenylthio)benzo[*d*]oxazole (6b)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6b** as a colorless oil (169 mg, yield = 70%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.66-7.64 (m, 2H), 7.39-7.37 (m, 4H), 7.21 (d, 1H, *J* = 8.0 Hz), 6.99 (d, 1H, *J* = 8.0 Hz), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 162.0, 149.1, 141.1, 133.2, 133.1, 128.7, 128.5, 126.4, 124.3, 118.0, 108.4, 20.4. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{12}NOS$ (242.0634), found: 242.0639.

6-Methyl-2-(phenylthio)benzo[*d*]oxazole (6c)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6c** as a white solid (169 mg, yield = 70%). m.p.: 56-58 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.67-7.64 (m, 2H), 7.46-7.39 (m, 4H), 7.16 (s, 1H), 7.04 (d, 1H, *J* = 8.0 Hz), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 162.3, 152.2, 139.8, 134.8, 134.2, 129.7, 129.6, 127.5, 125.5, 118.5, 110.3, 21.7. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{12}NOS$ (242.0634), found: 242.0629.

4-Methyl-2-(phenylthio)benzo[*d*]oxazole (6d)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6d** as a red oil (205 mg, yield = 85%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.60 (t, 2H, *J* = 4.0 Hz), 7.29 (s, 3H), 7.09 (d, 1H, *J* = 8.0 Hz), 7.03-6.95 (m, 2H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 161.4, 151.6, 141.3, 134.0, 129.6, 129.5, 129.5, 127.8, 125.1, 124.2, 107.4, 16.5. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{12}NOS$ (242.0634), found: 242.0642.

5-Fluoro-2-(phenylthio)benzo[*d*]oxazole (6e)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6e** as a yellow oil (113 mg, yield = 46%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.68-7.66 (m, 2H), 7.43-7.40 (m, 3H), 7.27-7.23 (m, 2H), 6.94-6.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 164.4, 158.9 (d, *J* = 239 Hz), 147.1, 141.8 (d, *J* = 13 Hz), 133.5, 129.0, 128.6, 125.6, 110.6 (d, *J* = 27 Hz), 109.1 (d, *J* = 10 Hz), 104.6 (d, *J* = 26 Hz). HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9FNOS$ (246.0484), found: 246.0477.

5-Chloro-2-(phenylthio)benzo[*d*]oxazole (6f)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6f** as a white solid (104 mg, yield = 40%). m.p.: 57-59 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.69-7.67 (m, 2H), 7.54 (d, 1H, *J* = 4.0 Hz), 7.46-7.42 (m, 3H), 7.26 (t, 1H, *J* = 8.0 Hz), 7.18-7.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 164.2, 149.3, 142.0, 133.6, 129.1, 128.9, 128.7, 125.5, 123.3, 117.9, 109.6. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9ClNOS$ (262.0088), found: 262.0081.

2-((4-Fluorophenyl)thio)benzo[*d*]oxazole (6g)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6g** as a colorless oil (174 mg, yield = 71%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.68-7.65 (m, 2H), 7.58-7.56 (m, 1H), 7.37 (d, 1H, *J* = 8.0 Hz), 7.25-7.18 (m, 2H), 7.12 (t, 2H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 162.8 (d, *J* = 250 Hz), 162.2, 162.2, 150.8, 140.9, 135.9 (d, *J* = 9.0 Hz), 123.3 (d, *J* = 12.0 Hz), 121.1 (d, *J* = 3.0 Hz), 118.0, 115.9 (d, *J* = 23 Hz), 109.0. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9FNOS$ (246.0384), found: 246.0388.

2-((4-Bromophenyl)thio)benzo[*d*]oxazole (6h)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6h** as a colorless oil (128 mg, yield = 42%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.49-7.43 (m, 5H), 7.28 (d, 1H, *J* = 8.0 Hz), 7.16-7.09 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 161.5, 150.8, 140.7, 134.8, 131.8, 125.1, 123.6, 123.5, 123.4, 118.1, 109.0. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9BrNOS$ (305.9583), found: 305.9589.

2-((4-Chlorophenyl)thio)benzo[*d*]oxazole (6i)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6i** as a colorless oil (78 mg, yield = 30%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.63-7.58 (m, 3H), 7.41-7.38 (m, 3H), 7.28-7.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 161.6, 150.8, 140.8, 135.3, 134.6, 128.8, 124.5, 123.4, 123.4, 118.1, 109.0. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9ClNOS$ (262.0088), found: 262.0082.

2-((4-(Trifluoromethyl)phenyl)thio)benzo[d]oxazole (6j)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6j** as a white solid

(198 mg, yield = 67%). m.p.: 40-42 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.67 (d, 2H, *J* = 8.0 Hz), 7.55-7.48 (m, 3H), 7.30-7.28 (m, 1H), 7.17-7.11 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 160.5, 150.8, 140.6, 132.6, 131.3, 130.4 (q, *J* = 32.0 Hz), 125.3 (q, *J* = 4.0 Hz), 123.7, 133.6, 122.6 (q, *J* = 270.0 Hz), 118.2, 109.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_9F_3NOS$ (296.0352), found: 296.0356.

2-((3-Bromophenyl)thio)benzo[*d*]oxazole (6k)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6k** as a white solid (174 mg, yield = 57%). m.p.: 58-60 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.81 (s, 1H), 7.58 (d, 2H, *J* = 4.0 Hz), 7.50 (d, 1H, *J* = 8.0 Hz), 7.36 (d, 1H, *J* = 8.0 Hz), 7.25-7.18 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 161.1, 150.8, 140.8, 135.5, 131.8, 131.7, 129.8, 128.2, 123.5, 123.5, 122.1, 118.2, 109.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9BrNOS$ (305.9583), found: 305.9578.

2-((2-Chlorophenyl)thio)benzo[*d*]oxazole (6l)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6l** as a white solid (151 mg, yield = 58%). m.p.: 44-46 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.78-7.76 (m, 1H), 7.63-7.60 (m, 1H), 7.54-7.52 (m, 1H), 7.42-7.24 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 160.6, 150.8, 140.9, 137.1, 135.1, 130.2, 129.5, 126.7, 125.9, 123.4, 118.1, 109.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_9ClNOS$ (262.0088), found: 262.0081.

2-(*o*-Tolylthio)benzo[d]oxazole (6m)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6m** as a colorless oil (142 mg, yield = 59%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.59 (d, 1H, *J*

= 4.0 Hz), 7.47 (d, 1H, *J* = 8.0 Hz), 7.29-7.23 (m, 3H), 7.16-7.08 (m, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 162.2, 150.8, 141.5, 141.0, 135.1, 130.2, 129.6, 126.1, 125.2, 123.3, 123.1, 117.9, 108.9, 20.0. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{12}NOS$ (242.0634), found: 242.0629.

2-((4-Methoxyphenyl)thio)benzo[*d*]oxazole (6n)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6n** as a colorless oil (149 mg, yield = 58%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.61-7.55 (m, 3H), 7.35 (d, 1H, *J* = 8.0 Hz), 7.23-7.15 (m, 2H), 6.94 (d, 2H, *J* = 8.0 Hz), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 164.4, 161.2, 151.9, 142.1, 136.7, 124.3, 124.0, 118.9, 117.0, 115.3, 109.9, 55.4. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{12}NO_2S$ (258.0583), found: 258.0587.

2-((3,4-Dimethylphenyl)thio)benzo[*d*]oxazole (6o)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6o** as a colorless oil (168 mg, yield = 66%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.55 (d, 1H, *J* = 8.0 Hz), 7.40 (t, 2H, *J* = 8.0 Hz), 7.32 (d, 1H, *J* = 8.0 Hz), 7.21-7.13 (m, 3H), 2.23 (s, 3H,), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 164.1, 151.9, 142.1, 139.1, 138.2, 135.7, 132.3, 131.0, 124.3, 124.1, 123.4, 119.0, 110.0, 19.8, 19.7. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{15}H_{14}NOS$ (256.0792), found: 256.0798.

2-(*p*-Tolylthio)benzo[*d*]oxazole (6p)

According to **TP2**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give the target compound **6p** as a colorless oil (101 mg, yield = 42%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.57 (d, 3H, *J* = 8.0 Hz), 7.38-7.35 (m, 1H), 7.24-7.17 (m, 4H), 2.37 (s, 3H). ^{13}C NMR (100 MHz,

CDCl$_3$, TMS): δ (ppm) 162.8, 150.9, 141.0, 139.3, 133.6, 129.4, 123.3, 123.1, 122.3, 118.0, 108.9, 20.3. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{14}H_{12}NOS$ (242.0634), found: 242.0639.

ASSOCIATED CONTENT

The Supporting Information (^1H, ^{13}C NMR spectra for the products) is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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