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One-pot Synthesis of 2-Benzyl/2-Allyl Substituted Thiobenzoazoles Using Transition-metal-free Conditions in Water

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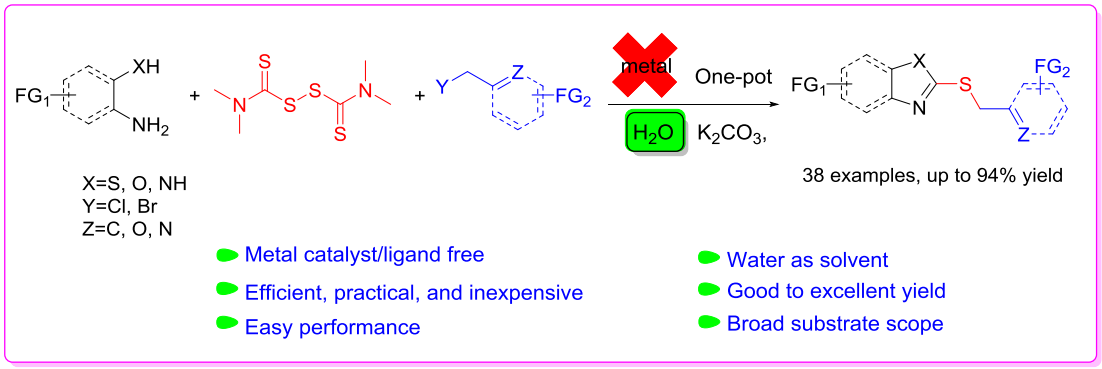


ABSTRACT

A transition-metal-free protocol for the one-pot synthesis of 2-benzyl/2-allyl substituted thiobenzoazoles in water was developed. The cyclization of 2-aminothiophenols, 2-aminophenols, and 1,2-phenylenediamines with tetramethylthiuram disulfide (TMTD) gave mercapto benzoheterocycles, the subsequent C-S coupling with benzyl or allyl halides furnished the desired products in good to excellent yields. This method features transition-metal free, water as solvent, easy performance, mild reaction conditions, wide substrate scope, and good to excellent yields, thus paves an efficient and useful way to establish the library of potentially active drug molecules.

INTRODUCTION

Phenyl heterocycles are key blocks in active drug molecules due to their pharmaceutical activity in medicinal chemistry studies.[1-4] Among these, 2-benzyl substituted thiobenzoazoles compounds are the skeleton of natural macromolecular compounds such as compound **1** (multidrug resistance in cancer chemtherapy), compounds **2** (proton-pump inhibitor which reduces stomach acid), compound **3** (antagonizing the activity of CCR3 receptors), and compound **4** (potential antifungal agent) (Fig.1).[5-10] These compounds exhibit excellent physiological activity, high bioselectivity and low physiological toxicity in the fungal growth inhibition test.[11] Thus, 2-benzyl substituted thiobenzoazoles have been paid extensive attention by the synthetic and medicinal chemists.[12-16]

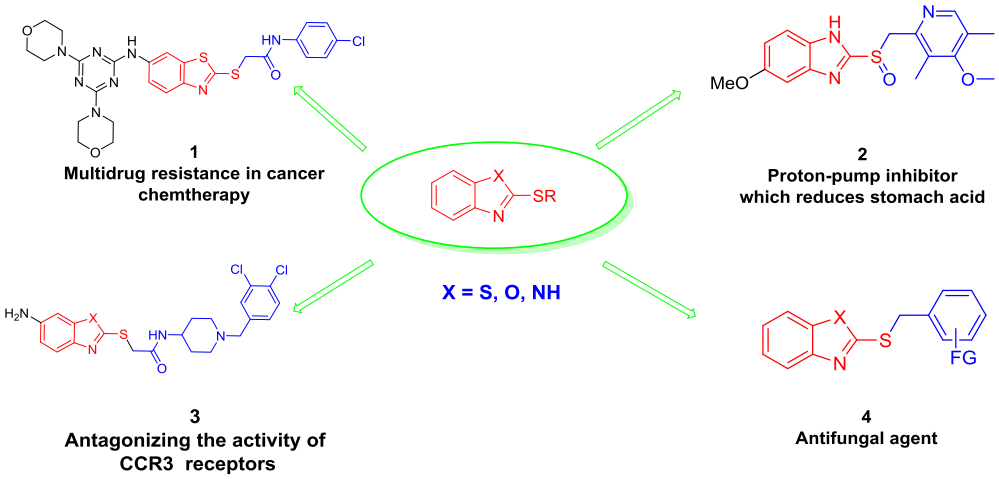
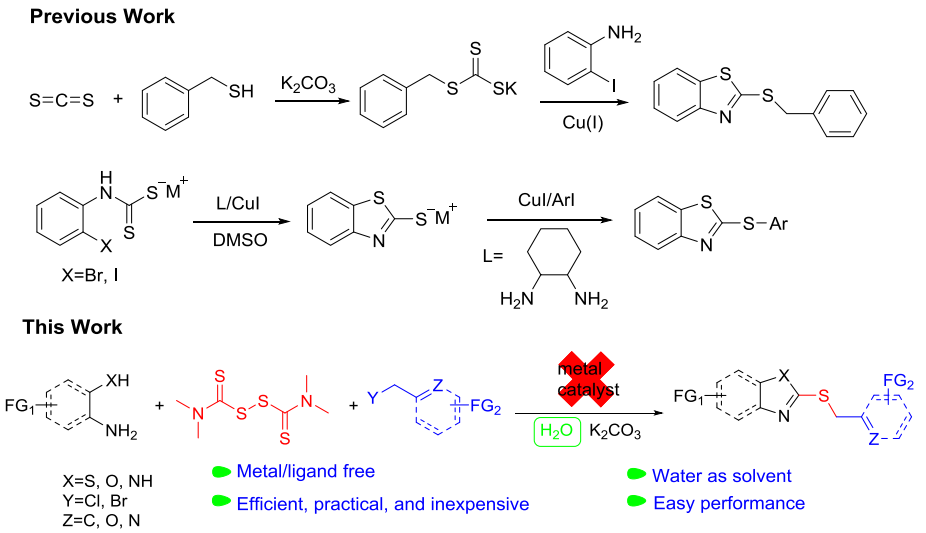


Figure 1. Representative drugs containing 2-allyl and 2-benzyl substituted thiobenzoazoles skeletons.

So far, there are numbers of ways to synthesize 2-benzyl substituted thiobenzoazoles,[17-20] while most of them use 2-mercaptobenzoic heterocycles as starting materials, which greatly limits the suitability of the substrates. Furthermore,

these methods suffer from disadvantages such as using organic solvents, the requirement of stoichiometric metal catalysts and highly toxic reagents (Scheme 1).



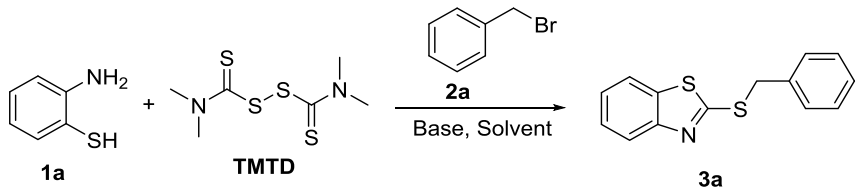
Scheme 1. Existing synthetic route and our strategy for the synthesis of 2-benzyl/2-allyl substituted thiobenzoazoles.

In addition, tandem or one-pot synthetic strategies have received great attention from the organic chemistry community in recent decades, because there is no need to separate the intermediates, thus might increase the yields of the final products.[21-23] Recently, we found that thiuram disulfides were very useful starting materials from an environmental point of view,[24] and also served as interesting vulcanization reagents for the development of new synthetic transformations.[25] Hereby, we would like to report an efficient and useful method for the one-pot synthesis of 2-benzyl/2-allyl substituted thiobenzoazoles using metal-free condition in water. The cyclization of 2-aminothiophenols, 2-aminophenols, and 1,2-phenylenediamines with tetramethylthiuram disulfide (TMTD) give mercapto benzoheterocycles, and the subsequent C-S coupling with benzyl or allyl halides might furnish the desired products (Scheme 1).

RESULTS AND DISCUSSION

By taking the strategy mentioned above, 2-aminothiophenol (**1a**), tetramethylthiuram disulfide (TMTD) and benzyl bromide (**2a**) were selected as substrates for the model reaction. 2-Aminothiophenol was firstly treated with TMTD in water at 120 ^{o}C for 2 h, base and benzyl bromide were then added before heating. The reaction conditions were examined, and the results are summarized in Table 1. Firstly, various bases such as KOH, NaOH, Na_2CO_3, K_2CO_3, Cs_2CO_3, $NaHCO_3$, pyridine, triethylamine and diethylamine were evaluated (entries 1-10) and K_2CO_3 was found to be the most suitable base to give the product in 94% yield. Next, different reaction temperatures (for the second step) were screened (entries 4, 11-14) and 80 ^{o}C was found to be the most suitable temperature. The substrate ratio (**1a** : TMTD : **2a**) was also explored (entries 4, 15-17) and it revealed that **1a** : TMTD: **2a** = 1 : 0.6 : 1 was the optimal substrate ratio. Furthermore, we studied the effects of solvents (entries 4, 18-22) and it was found that water was the best solvent. The optimal reaction conditions were summarized in entry 4.

Table 1. Reaction condition screening for the tandem synthesis of 2-arylthiobenzothiazole starting from 2-aminobenzenethiol, tetramethylthiuram disulfide (TMTD), and benzyl bromide [a]



Entry	base	T(^{o}C)[b]	Ratio[c]	Solvent	Yield(%)[d]
1	KOH	80	1:0.6:1	H_2O	89
2	NaOH	80	1:0.6:1	H_2O	86

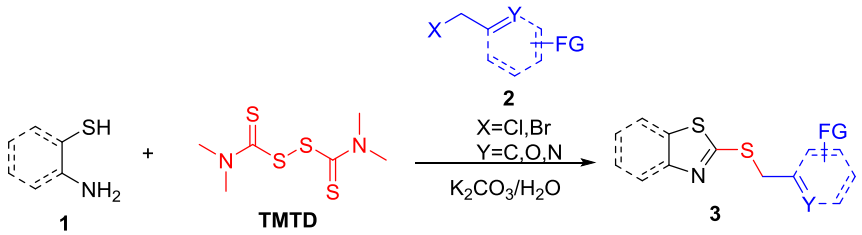
3	Na_2CO_3	80	1:0.6:1	H_2O	76
4	**K_2CO_3**	**80**	**1:0.6:1**	**H_2O**	**94, 88[e]**
5	Cs_2CO_3	80	1:0.6:1	H_2O	84
6	$NaHCO_3$	80	1:0.6:1	H_2O	63
7	Pyridine	80	1:0.6:1	H_2O	56
8	Triethylamine	80	1:0.6:1	H_2O	73
9	Diethylamine	80	1:0.6:1	H_2O	76
10	--	80	1:0.6:1	H_2O	80
11	K_2CO_3	110	1:0.6:1	H_2O	93
12	K_2CO_3	100	1:0.6:1	H_2O	91
13	K_2CO_3	60	1:0.6:1	H_2O	73
14	K_2CO_3	40	1:0.6:1	H_2O	51
15	K_2CO_3	80	1:0.6:0.6	H_2O	43
16	K_2CO_3	80	1:0.6:0.8	H_2O	75
17	K_2CO_3	80	1:0.6:1.1	H_2O	95
18	K_2CO_3	80	1:0.6:1	DMF	90
19	K_2CO_3	80	1:0.6:1	DMSO	60
20	K_2CO_3	80	1:0.6:1	EtOH	18
21	K_2CO_3	80	1:0.6:1	MeOH	13
22	K_2CO_3	80	1:0.6:1	DMAc	73

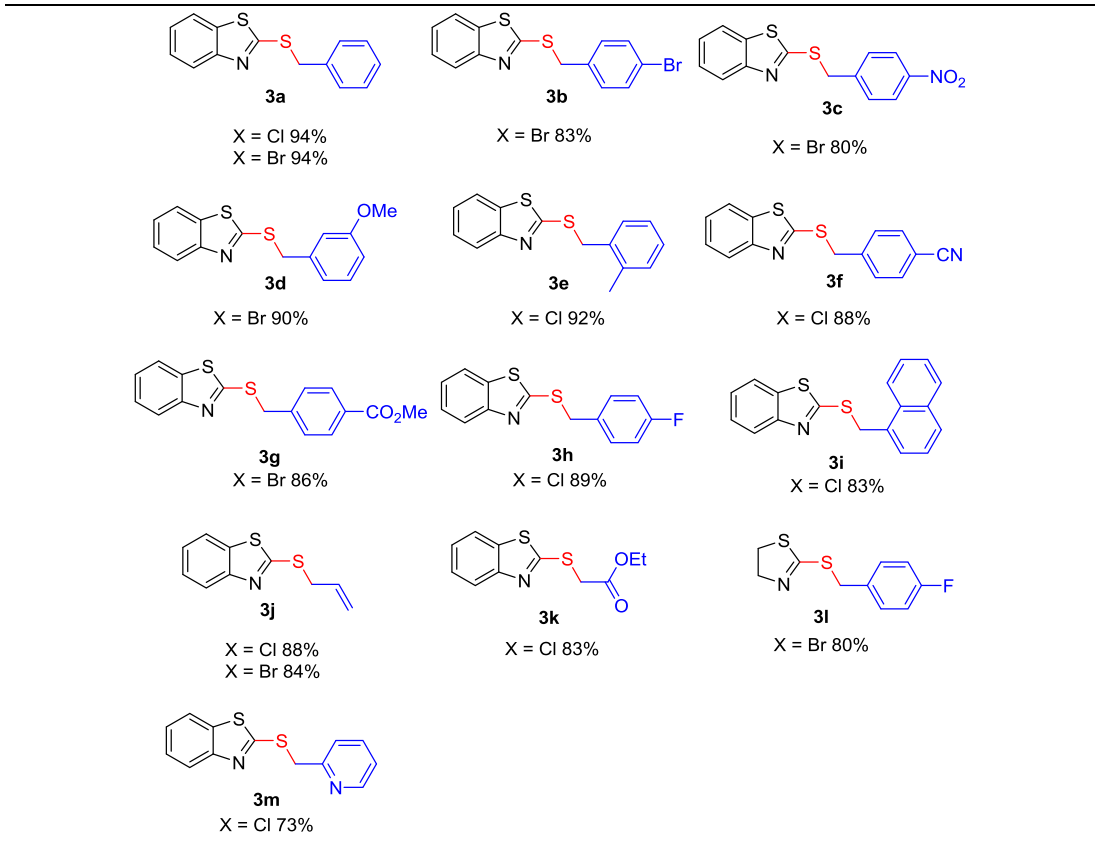
[a] Reaction conditions: **1a** (1.0 mmol), TMTD (0.6 mmol) and **2a** (1.0 mmol) in 2 mL of H_2O, the mixture of **1a** and TMTD was stirred for 2-3 h before the base and **2a** were added. [b] The temperature for the second step. [c] Mole ratio of **1a** : TMTD: **2a**. [d] Isolated yield based on **1a**. [e] A scaled-up reaction (10 mmol) was performed.

Having the optimized reaction conditions in hand, the substrates scope was

surveyed. Firstly, we examined the reactivity of benzyl or allyl halides in the presence of *o*-aminothiophenol (Table 2). In general, the desired tandem reaction (cyclization then C-S coupling) products could be obtained in good to excellent yields. Benzyl halides bearing with electron-donating groups, such as -OMe or –Me furnished the products **3d** and **3e** in 90% and 92% yield, respectively. While electron-withdrawing groups on benzyl ring gave the products (**3b, 3c, 3f, 3g, 3h, 3l**) in slightly lower yields. Sensitive ester group on the aryl ring could be tolerated well (**3g**). Ethyl chloroacetate (allyl-like structure) was also suitable for the C-S coupling to give the product **3k** in 83 % yield. We were also pleased to find that the non-aromatic ring substrate could be transformed to **3l** in good yield (80%).

Table 2. One-pot synthesis of 2-(benzylthio)benzo[*d*]thiazoles starting from *o*-aminothiophenol and tetramethylthiuram disulfide (TMTD) [a]

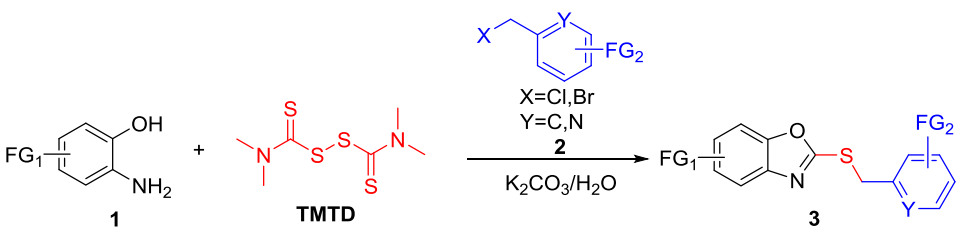


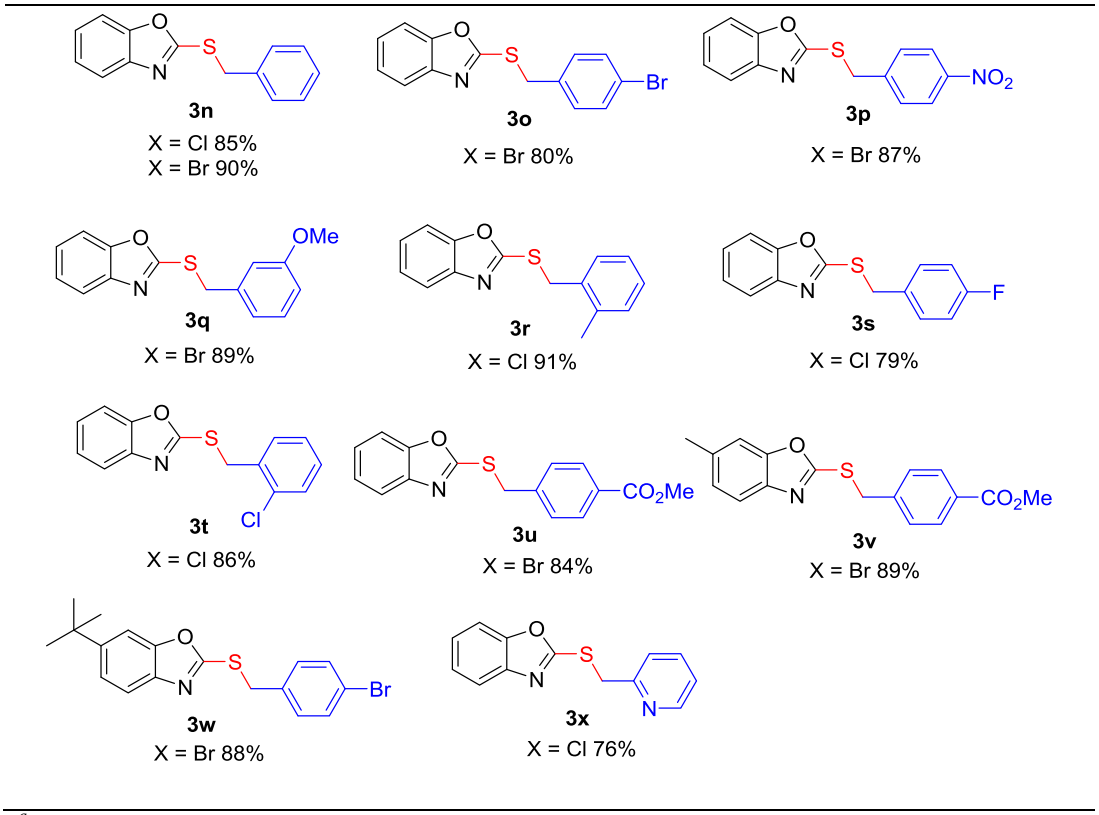


[a] Reaction conditions: A mixture of **1** (1.0 mmol) and tetramethylthiuram disulfide (0.6 mmol) in H_2O (2.0 mL) was stirred at 120 °C for 2-3 h, then K_2CO_3 (2.0 mmol) and **2** (1.0 mmol) were added and the mixture was stirred at 80 °C for 1h.

Next, we investigated the reactivity of a set of benzyl halides in the presence of *o*-aminophenols (Table 3). Similarly, the desired tandem reaction occurred smoothly and gave the desired products in good to excellent yields. The ester group could be also tolerated in the base condition (**3t, 3u**).

Table 3. One-pot synthesis of 2-(benzylthio)benzo[*d*]oxazoles starting from *o*-aminophenols and tetramethylthiuram disulfide (TMTD) [a]

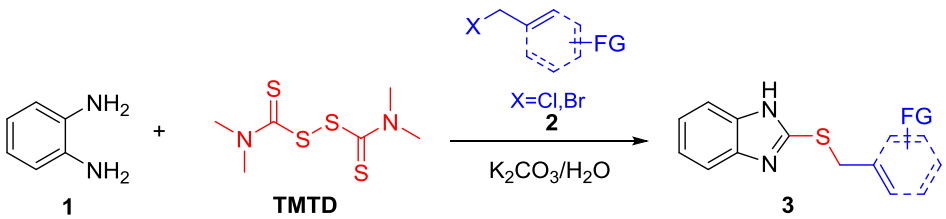


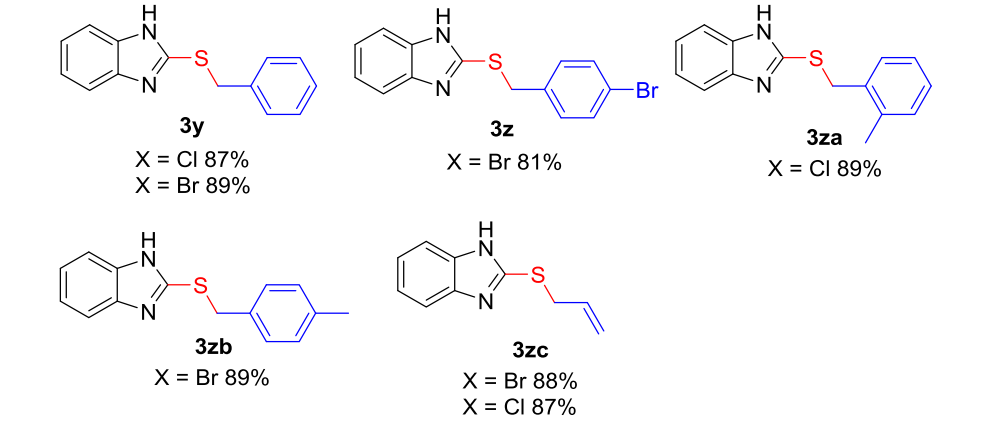


[a] Reaction conditions: A mixture of **1** (1.0 mmol) and tetramethylthiuram disulfide (0.6 mmol) in H_2O (2.0 mL) was stirred at 80 °C for 2-3 h, then K_2CO_3 (2.0 mmol) and **2** (1.0 mmol) were added and the mixture was stirred at 80 °C for 1h.

Furthermore, the reactivity of a set of benzyl/allyl halides in the presence of *o*-phenylenediamine was investigated (Table 4). The results showed that the desired products were furnished successfully under the standard reaction conditions. Ethyl chloroacetate was also submitted for the C-S coupling, but no product was obtained.

Table 4. One-pot synthesis of 2-(benzylthio)-*1H*-benzo[*d*]imidazole starting from *o*-phenylenediamine and tetramethylthiuram disulfide (TMTD) [a]

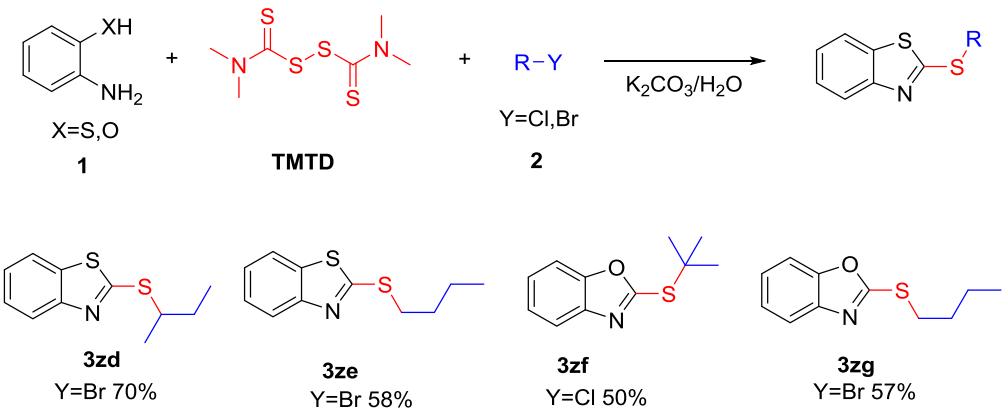




[a] Reaction conditions: A mixture of **1** (1.0 mmol) and tetramethylthiuram disulfide (0.6 mmol) in H_2O (2.0 mL) was stirred at 110 °C for 2-3 h, then K_2CO_3 (2.0 mmol) and **2** (1.0 mmol) were added and the mixture was stirred at 80 °C for 1h.

Moreover, halogenated alkanes were also submitted for the tandem reactions. Gratifyingly, the target products could be achieved in 50-70% yield (Table 5), showing its broad substrate compatibility.

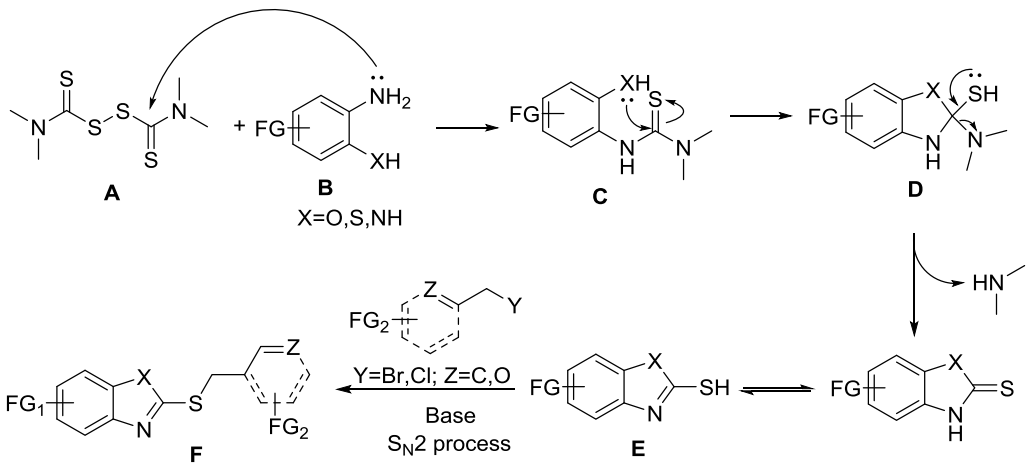
Table 5. One-pot synthesis of 2-(alkylthio)benzo[*d*]thiazole by using alkyl halides as starting materials [a]



[a] Reaction conditions: A mixture of **1** (1.0 mmol) and tetramethylthiuram disulfide (0.6 mmol) in H_2O (2.0 mL) was stirred at 120 °C (X=S) or 80 °C (X=O) for 2-3 h, then K_2CO_3 (2.0 mmol) and **2** (1.0 mmol) were added and the mixture was stirred at 80 °C for 1h.

The results obtained form Table 2-Table 5 showed that this protocol had good substrate adaptability, which might provide an easy and convenient access to the establishment of drug molecule library for the pharmaceutical industry.

Based on the experimental results and our previous effort on the organosulfur chemistry,[24] a plausible reaction pathway is outlined in Scheme 2. Tetramethylthiuram disulfide (TMTD) **A** reacts with aniline **B** to give intermediate thiourea **C**, and the XH (X = O, S, NH) group of **C** undergoes intramolecular nucleophilic addition forming intermediate **D**. **D** undergoes intramolecular elimination by removing dimethylamine gas, forming mercapto benzoheterocycle **E**. The subsequent S_N2 process with benzyl/allyl bromide allow **E** to give the final C-S coupling product **F** smoothly.



Scheme 2. Plausible mechanism of the reaction.

CONCLUSION

In summary, we have developed a convenient, highly efficient and one-pot green synthetic method for the synthesis of 2-benzyl/2-allyl substituted thiobenzoazoles in water. The cyclization of 2-aminothiophenols, 2-aminophenols, and

1,2-phenylenediamines with tetramethylthiuram disulfide (TMTD) gave mercapto benzoheterocycles, and the subsequent C-S coupling with benzyl or allyl halides furnished the desired products in good to excellent yields. This method features transition-metal free, water as solvent, easy performance, mild reaction conditions, wide substrate scope, and good to excellent yields, illustrating its practical synthetic value in some potentially biologically active compounds, especially for the establishment of molecule library. Further details and the development of related applications for this protocol are under research in our laboratory.

EXPERIMENTAL SECTION

General Procedures

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 $CDCl_3$ or DMSO-d_6 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 PE (petroleum ether)-EtOAc as eluent.

Typical Procedure (TP) for Synthesis of 2-(benzylthio)benzothiazole (3a). A mixture of 2-aminobenzenethiol (**1a**, 1.0 mmol) and tetramethylthiuram disulfide (TMTD, 0.6 mmol) in H_2O (2.0 mL) was stirred at 120 ^{o}C for 2-3 h before K_2CO_3

(2.0 mmol) and benzyl bromide (**2a**, 1.0 mmol) were added. The resultant mixture was heated at 80 ^{o}C and checked by TLC until the starting material was finished (about 1h). The reaction was cooled down to room temperature, quenched with sat. NH_4Cl solution (5 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 **3a**.

Analytical data of products

2-(Benzylthio)benzo[*d*]thiazole (3a).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3a** as a colorless oil (242 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.82 (d, *J*= 8.0 Hz, 1H), 7.67-7.64 (m, 1H), 7.38-7.31 (m, 3H), 7.28-7.16 (m, 4H), 4.52 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 165.3, 152.1, 135.1, 134.3, 128.0, 127.6, 126.7, 125.0, 123.2, 120.5, 119.9, 36.7. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{12}NS_2$ (258.0406), found: 258.0403.

2-((4-Bromobenzyl)thio)benzo[*d*]thiazole (3b).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3b** as a white solid (278 mg 83%). Mp: (76-79 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.73(d, 1H, *J*= 8.0 Hz), 7.51 (d, *J*= 8.0 Hz, 1H), 7.24-7.20 (m, 3H), 7.11-7.06 (m, 3H), 7.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 165.84, 153.14, 135.59, 135.46, 131.83, 130.89, 126.21, 124.49, 121.80, 121.68, 121.15, 36.97. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{11}BrNS_2$ (335.9511), found: 335.9514.

2-((4-Nitrobenzyl)thio)benzo[*d*]thiazole (3c).

According to **TP**, the residue was purified by flash chromatography on silica gel

(petroleum ether/ethyl acetate = 15:1) to give the target compound **3c** as a white solid (242 mg, 80%). Mp: (89-91 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 8.01 (d, *J*= 12.0 Hz, 2H), 7.77 (d, *J*= 8.0 Hz, 1H), 7.61 (d, *J*= 8.0 Hz, 1H), 7.49 (d, *J*= 8.0 Hz, 2H), 7.31 (t, *J*= 8.0 Hz, 1H), 7.20-7.14 (m, 1H), 4.52 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 163.7, 151.8, 146.2, 143.4, 134.3, 128.9, 125.1, 123.5, 122.7, 120.5, 120.0, 35.3. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{11}N_2O_2S_2$ (303.0256), found: 303.0251.

2-((3-Methoxybenzyl)thio)benzo[*d*]thiazole (3d).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 50:1) to give the target compound **3d** as a yellow oil (259 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.81 (d, *J*= 8.0 Hz, 1H), 7.65 (d, *J*= 8.0 Hz, 1H), 7.35-7.31 (m, 1H), 7.22-7.13 (m, 2H), 6.94 (d, *J*= 8.0 Hz, 2H), 6.74-6.71 (m, 1H), 4.48 (s, 2H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 166.4, 159.7, 153.1, 137.6, 135.3, 129.7, 126.1, 124.3, 121.5, 121.4, 121.0, 114.6, 113.4, 55.2, 37.7. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{15}H_{14}NOS_2$ (288.0511), found: 288.0516.

2-((2-Methylbenzyl)thio)benzo[*d*]thiazole (3e).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3e** as a colorless oil (250 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.89 (d, *J*= 8.0 Hz, 1H), 7.58 (d, *J*= 12.0 Hz, 1H), 7.30-7.23 (m, 2H), 7.14 (t, *J*= 8.0 Hz, 1H), 7.07-7.00 (m, 3H), 4.50 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 166.6, 153.2, 137.2, 135.3, 133.7, 130.7, 130.2, 128.2, 126.3, 126.1, 124.3, 121.6, 121.0, 36.0, 19.3. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{15}H_{14}NS_2$ (272.0562), found: 272.0560.

4-((Benzo[*d*]thiazol-2-ylthio)methyl)benzonitrile (3f).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3f** as a yellow solid (249 mg, 88%). Mp: (63-65 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.71 (d, *J*= 8.0 Hz, 1H), 7.52 (d, *J*= 8.0 Hz, 1H), 7.33 (s, 4H), 7.23 (t, *J*= 8.0 Hz, 1H), 7.19 (t, *J*= 8.0 Hz, 1H), 4.38 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 165.0, 152.9, 142.3, 135.4, 132.3, 129.8, 126.2, 124.6, 121.6, 121.1, 118.6, 111.4, 36.8. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{15}H_{11}N_2S_2$ (283.0358), found: 283.0351.

Methyl 4-((benzo[*d*]thiazol-2-ylthio)methyl)benzoate (3g).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3g** as a colorless solid (271 mg, 86%). Mp: (105-106 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.86 (d, *J*= 8.0 Hz, 2H), 7.77 (d, *J*= 8.0 Hz, 1H), 7.60 (d, *J*= 8.0 Hz, 1H), 7.39 (d, *J*= 8.0 Hz, 2H), 7.29 (t, *J*= 8.0 Hz, 1H), 7.16 (t, *J*= 8.0 Hz, 1H), 4.49 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 166.6, 165.5, 153.0, 141.7, 135.4, 129.9, 129.5, 129.1, 126.1, 124.4, 121.6, 121.0, 52.1, 37.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{16}H_{14}NO_2S_2$ (316.0460), found: 316.0466.

2-((4-Fluorobenzyl)thio)benzo[*d*]thiazole (3h).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3h** as a yellow solid (246 mg, 89%). Mp: (47-49 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.81 (d, *J*= 8.0 Hz, 1H), 7.64 (d, *J*= 8.0 Hz, 1H), 7.35-7.30 (m, 3H), 7.22-7.15 (m, 1H), 6.94-6.88 (m, 2H), 4.47 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 164.9, 162.4, 159.9, 152.0, 134.2, 131.0 (d, *J* = 3.2 Hz), 129.7 (d, *J* = 8.2 Hz), 125.0, 123.3, 120.4, 119.9, 114.5 (d, *J* = 21.6 Hz), 35.7. HRMS *m*/*z* $[M+H]^+$ (ESI) Calcd for

$C_{14}H_{11}FNS_2$ (276.0311), found: 276.0308.

2-((Naphthalen-1-ylmethyl)thio)benzo[*d*]thiazole (3i).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3i** as a yellow oil (256 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 8.01 (d, *J*= 8.0 Hz, 1H), 7.83 (d, *J*= 8.0 Hz, 1H), 7.72 (d, *J*= 8.0 Hz, 1H), 7.65 (d, *J*= 8.0 Hz, 1H), 7.58 (d, *J*= 8.0 Hz, 1H), 7.48 (d, *J*= 8.0 Hz, 1H), 7.42-7.23 (m, 4H), 7.16-7.08 (m, 1H), 4.96 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 166.6, 153.2, 135.4, 134.0, 131.6, 131.5, 129.0, 128.1, 126.6, 126.1, 126.1, 125.4, 124.4, 123.7, 121.6, 121.1, 35.7. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{18}H_{14}NS_2$ (308.0562), found: 308.0560.

2-(Allylthio)benzo[*d*]thiazole (3j).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3j** as a yellow oil (183 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.75 (d, *J*= 8.0 Hz, 1H), 7.69 (d, *J*= 8.0 Hz, 1H), 7.27 (t, *J*= 8.0 Hz, 1H), 7.14 (t, *J*= 8.0 Hz, 1H), 5.92-5.85 (m, 1H), 5.27-5.22 (m, 1H), 5.06 (d, *J*= 8.0 Hz, 1H), 3.85 (d, *J*= 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 165.1, 152.0, 134.2, 131.2, 124.9, 123.1, 120.4, 119.8, 118.1, 35.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{10}H_{10}NS_2$ (208.0249), found: 208.0244.

Ethyl 2-(benzo[*d*]thiazol-2-ylthio)acetate (3k).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3k** as a yellow oil (211 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.77 (d, *J*= 8.0 Hz, 1H), 7.67 (d, *J*= 8.0 Hz, 1H), 7.33 (t, *J*= 8.0 Hz, 1H), 7.24-7.18 (m, 1H), 4.19-4.14 (m, 2H), 4.09 (s, 2H), 1.21 (t, *J*= 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm)

167.2, 163.7, 151.8, 134.4, 125.0, 123.4, 120.6, 120.0, 61.0, 34.1, 13.0. HRMS *m*/*z* $[M+H]^+$ (ESI) Calcd for $C_{11}H_{12}NO_2S_2$ (254.0304), found: 254.0309.

2-((4-Fluorobenzyl)thio)-4,5-dihydrothiazole (3l).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3l** as a yellow oil (182 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.25-7.22 (m, 2H), 6.89 (t, *J*= 8.0 Hz, 2H), 4.23 (s, 2H), 4.12 (t, *J*= 8.0 Hz, 1H), 3.29 (t, *J*= 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 163.8, 162.2, 159.8, 131.5 (d, *J* = 3.3 Hz), 129.6 (d, *J* = 8.2 Hz), 114.3 (d, *J* = 21.5 Hz), 63.1, 34.8 (d, *J* = 39.2 Hz). HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{10}H_{11}FNS_2$ (228.0311), found: 228.0312.

2-((Pyridin-2-ylmethyl)thio)benzo[*d*]thiazole (3m).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to give the target compound **3m** as a yellow oil (188 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 8.45 (d, *J* = 4.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 4.64 (s, 2H). δ (ppm). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 165.0, 155.3, 151.9, 148.4, 135.7, 134.3, 124.9, 123.2, 122.3, 121.4, 120.4, 119.9, 38.0. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_{11}N_2S_2$ (259.0358), found: 259.0359.

2-(Benzylthio)benzo[*d*]oxazole (3n).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3n** as a yellow oil (218 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.50 (d, *J*= 8.0 Hz, 1H), 7.33-7.27 (m, 3H), 7.21-7.06 (m, 5H), 4.42 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 164.6, 151.9, 141.9, 135.9, 129.1, 128.8, 128.0, 124.39 124.0, 118.5,

109.9, 36.6. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{14}H_{12}NOS$ (242.0634), found: 242.0637.

2-((4-Bromobenzyl)thio)benzo[*d*]oxazole (3o).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to give the target compound **3o** as a yellow oil (256 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.45 (d, *J*= 4.0 Hz, 1H), 7.22 (t, *J*= 8.0 Hz, 3H), 7.13-7.01 (m, 4H), 4.28 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 164.1, 151.9, 141.8, 135.2, 131.8, 130.7, 124.4, 124.1, 121.9, 118.6, 110.0, 35.9. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{14}H_{11}BrNOS$ (319.9739), found: 319.9731.

2-((4-Nitrobenzyl)thio)benzo[*d*]oxazole (3p).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3p** as a white solid (250 mg, 87%). Mp: (113-115 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 8.09 (d, *J*= 8.0 Hz, 1H), 7.58-7.51 (m, 3H), 7.36-7.33 (m, 1H), 7.23-7.15 (m, 2H), 4.51 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 162.2, 150.9, 146.3, 142.9, 140.5, 128.9, 123.4, 123.2, 122.8, 117.5, 108.9, 34.4. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{14}H_{11}N_2O_3S$ (287.0485), found: 287.0480.

2-((3-Methoxybenzyl)thio)benzo[*d*]oxazole (3q).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3q** as a colorless oil (242 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.68-7.65 (m,1H), 7.50-7.46 (m, 1H), 7.34-7.27 (m, 3H), 7.10-7.06 (m, 2H), 6.90-6.86 (m, 1H), 4.59 (d, *J*= 4.0 Hz, 2H), 3.84 (d, *J*= 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 163.4, 158.7, 150.8, 140.8, 136.2, 128.7, 123.2, 122.9, 120.2, 117.3, 113.5, 112.4, 108.8, 54.1, 35.5. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{15}H_{14}NO_2S$ (272.0740), found:

272.0747.

2-((2-Methylbenzyl)thio)benzo[*d*]oxazole (3r).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3r** as a yellow oil (233 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.50 (d, *J*= 8.0 Hz, 1H), 7.29-7.26 (m, 2H), 7.16-7.00 (m, 5H), 4.45 (s, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 163.5, 150.7, 140.8, 136.0, 132.1, 129.5, 129.1, 127.2, 125.2, 123.2, 122.8, 117.3, 108.7, 33.8, 18.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{15}H_{14}NOS$ (256.0791), found: 256.0795.

2-((4-Fluorobenzyl)thio)benzo[*d*]thiazole (3s).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3s** as a yellow oil (205 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.37 (d, *J*= 8.0 Hz, 1H), 7.17-7.14 (m, 3H), 7.04-6.94 (m, 2H), 6.76-6.72 (m, 2H), 4.25 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 164.3, 163.6, 161.1, 151.9, 141.8, 131.8 (d, *J* = 3.3 Hz), 130.8 (d, *J* = 8.1 Hz), 124.2 (d, *J* = 34.7 Hz), 118.5, 115.6 (d, *J* = 21.6 Hz), 109.9 , 35.7. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{11}FNOS$ (260.0540), found: 260.0549.

2-((2-Chlorobenzyl)thio)benzo[*d*]oxazole (3t).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3t** as a yellow oil (237 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.45-7.41 (m, 2H), 7.22-7.17 (m, 2H), 7.10-6.98 (m, 4H) 4.47 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 164.4, 152.0, 141.9, 134.4, 134.0, 131.3, 129.7, 129.4, 127.1, 124.3, 124.0, 118.5, 109.9, 34.3. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{11}ClNOS$ (276.0244), found: 276.0240.

Methyl 4-((benzo[*d*]oxazol-2-ylthio)methyl)benzoate (3u).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3u** as a white solid (252 mg, 84%). Mp: (83-85 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.85 (d, *J*= 12.0 Hz, 2H), 7.48 (d, *J*= 4.0 Hz, 1H), 7.39 (d, *J*= 8.0 Hz, 2H), 7.27 (d, *J*= 8.0 Hz, 1H), 7.15-7.06 (m, 2H), 4.42 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 166.5, 163.9, 151.9, 141.8, 141.3, 129.9, 129.6, 129.0, 124.3, 124.0, 118.5, 109.9, 52.1, 36.0. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{16}H_{14}NO_3S$ (300.0689), found: 300.0681.

Methyl 4-(((6-methylbenzo[*d*]oxazol-2-yl)thio)methyl)benzoate (3v).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3v** as a brown solid (280 mg, 89%). Mp: (105-106 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.87-7.84 (m, 2H), 7.40-7.37 (m, 2H), 7.26 (s, 1H), 7.16-7.12 (m, 1H), 6.91-6.87 (m, 1H), 4.41 (d, *J*= 4.0 Hz, 2H), 3.76 (d, *J*= 4.0 Hz, 3H), 2.29 (d, *J*= 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 165.4, 162.6, 149.0, 140.8, 140.3, 133.0, 128.8, 128.8, 128.4, 127.9, 123.9, 117.4, 108.1, 51.0, 34.9, 20.3. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{17}H_{16}NO_3S$ (314.0845), found: 314.0849

2-((4-Bromobenzyl)thio)-6-(*t*-butyl)benzo[*d*]oxazole (3w).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3w** as a white soild (331 mg, 88%). Mp: (79-80 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.53 (s, 1H), 7.28 (d, *J*= 8.0 Hz, 2H), 7.21-7.14 (m, 4H), 4.33 (s, 2H), 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 164.0, 149.9, 147.9, 141.7, 135.3, 131.8, 130.7, 121.9, 121.6, 115.2, 109.1, 35.8, 34.9, 31.8. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for

$C_{18}H_{19}BrNOS$ (376.0365), found: 376.0361.

2-((Pyridin-2-ylmethyl)thio)benzo[*d*]oxazole (3x).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3x** as a white solid (184 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 8.48 (d, *J*= 4.0 Hz, 1H), 7.56-7.49 (m, 2H), 7.43 (d, *J*= 8.0 Hz, 1H), 7.32 (d, *J*= 8.0 Hz, 1H), 7.20-7.07 (m, 3H), 4.61 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 163.4, 154.8, 150.9, 148.5, 140.7, 135.8, 123.2, 122.8, 122.2, 121.5, 117.3, 108.8, 37.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{13}H_{11}N_2OS$ (243.0857), found: 243.0851.

2-(Benzylthio)-*1H*-benzo[*d*]imidazole (3y).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give the target compound **3y** as a white solid (215 mg, 89%). Mp: (184-185 ^{o}C). ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ (ppm) 12.54 (s, 1H), 7.45 (d, *J*= 8.0 Hz, 4H), 7.33-7.25 (m, 3H), 7.15-7.12 (m, 2H), 4.58 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ (ppm) δ 150.1, 138.1, 129.3, 128.9, 127.7, 121.8, 35.6. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{13}N_2S$ (241.0794), found: 241.0790.

2-((4-Bromobenzyl)thio)-*1H*-benzo[*d*]imidazole (3z).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give the target compound **3z** as a white solid (258 mg, 81%). Mp: (187-188 ^{o}C). ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ (ppm) 12.53 (s, 1H), 7.51-7.40 (m, 6H), 7.14-7.12 (m, 2H), 4.55 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ (ppm) 149.8, 137.9, 131.7, 131.4, 129.3, 128.9, 121.9, 120.8, 34.8. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{14}H_{12}BrN_2S$ (318.9899), found: 318.9902.

2-((2-Methylbenzyl)thio)-*1H*-benzo[*d*]imidazole (3za).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give the target compound **3za** as a white solid (227 mg, 89%). Mp: (161-163 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 9.43 (s, 1H), 7.74 (s, 1H), 7.34-7.12 (m, 6H), 4.60 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 148.8, 136.0, 133.2, 129.5, 129.0, 127.0, 125.2, 34.5, 18.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{15}H_{15}N_2S$ (255.0950), found: 255.0956.

2-((4-Methylbenzyl)thio)-*1H*-benzo[*d*]imidazole (3zb).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give the target compound **3zb** as a white solid (227 mg, 89%). Mp: (164-167 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 11.36 (s, 1H), 7.45-7.42 (m, 2H), 7.18-7.11 (m, 4H), 7.00 (d, *J*= 8.0 Hz, 2H), 4.42 (s, 2H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 148.9, 136.4, 132.4, 128.3, 127.8, 121.3, 36.1, 20.1. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{15}H_{15}N_2S$ (255.0950), found: 255.0951.

2-(Allylthio)-*1H*-benzo[*d*]imidazole (3zc).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give the target compound **3zc** as a white solid (167 mg, 88%). Mp: (140-141 ^{o}C). ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ (ppm) 12.54 (s, 1H), 7.43 (s, 2H), 7.14-7.10 (m, 2H), 6.06-5.95 (m, 1H), 5.31 (d, *J*= 16.0 Hz, 1H), 5.11 (d, *J*= 8.0 Hz, 1H), 3.96 (d, *J*= 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ (ppm) 149.8, 134.2, 121.8, 121.8, 118.5, 34.3. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{10}H_{10}N_2S$ (190.0565), found: 190.0566.

2-(*sec*-Butylthio)benzo[*d*]thiazole (3zd).

According to **TP**, the residue was purified by flash chromatography on silica gel

(petroleum ether/ethyl acetate = 15:1) to give the target compound **3zd** as a yellow oil (156 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.79 (d, *J*= 8.0 Hz, 1H), 7.66 (d, *J*= 8.0 Hz, 1H), 7.32 (t, *J*= 8.0 Hz, 1H), 7.20 (t, *J*= 8.0 Hz, 1H), 3.88-3.83 (m, 1H), 1.79-1.64 (m, 2H), 1.42 (d, *J*= 4.0 Hz, 3H), 0.98 (d, *J*= 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 166.7, 153.4, 135.3, 125.9, 124.2, 121.5, 120.9, 45.9, 29.7, 20.9, 11.4. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{11}H_{14}NS_2$ (224.0562), found: 224.0567.

2-(Butylthio)benzo[*d*]thiazole (3ze).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to give the target compound **3ze** as a yellow oil (129 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.76 (d, *J*= 8.0 Hz, 1H), 7.62 (d, *J*= 8.0 Hz, 1H), 7.31-7.27 (m, 1H), 7.18-7.14 (m, 1H), 3.23 (t, *J*= 8.0 Hz, 2H). 1.73-1.65 (m, 2H), 1.44-1.34 (m, 2H), 0.85 (t, *J*= 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 166.3, 152.2, 134.0, 124.9, 123.0, 120.3, 119.84, 32.2, 30.1, 20.8, 12.5. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{11}H_{14}NS_2$ (224.0562), found: 224.0567.

2-(*tert*-Butylthio)benzo[*d*]oxazole (3zf).

According to **TP**, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to give the target compound **3zf** as a yellow oil (103 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.30-7.28 (m, 1H), 7.23-7.14 (m, 3H), 2.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 170.7, 147.7, 124.1, 123.2, 109.4, 109.1, 50.6, 29.9. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{11}H_{14}NOS$ (208.0791), found: 208.0799.

2-(Butylthio)benzo[*d*]oxazole (3zg).

According to **TP**, the residue was purified by flash chromatography on silica gel

(petroleum ether/ethyl acetate = 15:1) to give the target compound **3zg** as a yellow oil (118 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ (ppm) 7.49 (d, *J*= 8.0 Hz, 1H), 7.31 (d, *J*= 8.0 Hz, 1H), 7.18-7.08 (m, 2H), 3.20 (t, *J*= 8.0 Hz, 1H), 1.74-1.66 (m, 2H), 1.44-1.34 (m, 2H), 0.85 (t, *J*= 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ (ppm) 164.1, 150.6, 140.9, 123.1, 122.6, 117.2, 108.7, 30.9, 30.1, 20.7, 12.5. HRMS (ESI) *m*/*z* $[M+H]^+$ Calcd for $C_{11}H_{14}NOS$ (208.0791), found: 208.0794.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization data, and ^{1}H, ^{13}C NMR spectra for new compound (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Boschelli, D. H.; Connor, D. T.; Bornemeier, D. A.; Dyer, R. D.; Kennedy, J. A.; Kuipers, P. J.; Okonkwo, G. C.; Schrier, D. J.; Wright, C. D. 1,3,4-Oxadiazole, 1,3,4-thiadiazole, and 1,2,4-triazole analogs of the fenamates: in vitro inhibition of cyclooxygenase and 5-lipoxygenase activities. *J. Med. Chem.* **1993**, *36*, 1802-1810.

(2) Kohli, P.; Srivastava, S. Synthesis and biological activity of mercaptobenzoxazole based thiazolidinones and their arylidenes. *J. Chin. Chem. Soc-Taip.* **2007**, *54*, 1003-1010.

(3) Paramashivappa, R.; Kumar, P. P.; Rao, P. S.; Rao, A. S. Design, synthesis and biological evaluation of benzimidazole/benzothiazole and benzoxazole derivatives as cyclooxygenase inhibitors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 657-660.

(4) Refaey, S.; Taha, F.; El-Malak, A. A. Inhibition of stainless steel pitting corrosion in acidic medium by 2-mercaptobenzoxazole. *Appl. Surf. Sci.* **2004**, *236*, 175-185.

(5) Chaney, M. O.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. Structure of A23187, a divalent cation ionophore. *J. Am. Chem. Soc.* **1974**, *96*, 1932-1933.

(6) (a) Kusumi, T.; Ooi, T.; Wülchli, M. R.; Kakisawa, H. Structure of the novel antibiotics boxazomycins A, B, and C. *J. Am. Chem. Soc.* **1988**, *110*, 2954-2958. (b) Block, E. The organosulfur chemistry of the genus Allium–implications for the organic chemistry of sulfur. *Angew. Chem. In. Ed.* **1992**, *31*, 1135-1178. (c) Zhang, S. Z.; Block, E.; Katz, L. C. Encoding social signals in the mouse main olfactory bulb. *Nature* **2005**, *434*, 470-477.

(7) Ovenden, S. P. B.; Nielson, J. L.; Liptrot, C. H.; Willis, R. H.; Tapiolas, D. M.; Wright, A. D.; Motti, C. A. Sesquiterpene benzoxazoles and sesquiterpene

quinones from the marine sponge Dactylospongia elegans. *J. Nat. Prod.* **2010**, *74*, 65-68.

(8) Varun, B. V.; Prabhu, K. R. Regioselective thiolation of arenes and heteroarenes: C–H functionalization strategy for C–S bond formation. *J. Org. Chem.* **2014**, *79*, 9655-9668.

(9) Liu, Y.; Kim, J.; Seo, H.; Park, S.; Chae, J. Copper (II) ‐ catalyzed single ‐ step synthesis of aryl thiols from aryl halides and 1, 2 ‐ ethanedithiol. *Adv. Synth. Catal.* **2015**, *357*, 2205-2212.

(10) (a) Maske, P. P.; Lokapure, S. G.; Nimbalkar, D.; Disouza, J. I. Synthesis and antiprotozoal activity of nitro and halogeno substituted some novel mercaptobenzimidazole derivatives. *Der Pharma Chemica* **2012**, *4*, 1283-1287. (b) Zhang, J.-T.; J. Feng, Q. H.; Dong, Z. WO2010048603,2010. (c) Choudhary, A. N.; Kumar, A.; Jural, V. Quantitative structure activity relationship (QSAR) analysis of substituted 4-oxothiazolidines and 5-arylidines as lipoxygenase inhibitors. *Mini-Rev. Med.Chem.* **2010**, *10*, 705-714. (d) Naya, A.; Kobayashi, K.; Ishikawa, M.; Ohwaki, K.; Saeki, T.; Noguchi, K.; Ohtake, N. Discovery of a novel CCR3 selective antagonist. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1219-1223. (e) Murphy, A. R.; Fréchet, J. M. J. Organic semiconducting oligomers for use in thin film transistors. *Chem. Rev.* **2007**, *107*, 1066-1096.

(11) Ballari, M. S.; Cano, H. N.; Lopez, A. G.; Wunderlin, D. A.; Feresin, G.; Santiago, A. N. Green synthesis of potential antifungal agents: 2-benzyl substituted thiobenzoazoles. *J. Agric Food Chem.* **2017**, *65*, 10325-10331.

(12) Demmer, C. S.; Bunch, L. Benzoxazoles and oxazolopyridines in medicinal chemistry studies. *Eur. J. Med. Chem.* **2015**, *97*, 778-785.

(13) Ballabeni, M.; Ballini, R.; Bigi, F.; Maggi, R.; Parrini, M.; Predieri, G.; Sartori, G.

Synthesis of symmetrical N, N'-disubstituted thioureas and heterocyclic thiones from amines and CS_2 over a ZnO/Al_2O_3 composite as heterogeneous and reusable catalyst. *J. Org. Chem*. **1999**, *64*, 1029-1032.

(14) Deligeorgiev, T. G.; Kaloyanova, S. S.; Lesev, N. Y.; Vaquero, J. J. An environmentally benign procedure for the synthesis of substituted 2-thiobenzothiazoles, 2-thiobenzoxazoles, 2-thiobenzimidazoles, and 1, 3-oxazolopyridine-2-thiols. *Monatsh. Chem.* **2011**, *142*, 895-899.

(15) Li, Z.; Liu, D.; Chen, Y.; Yin, Y.; Wang, Z.; Sun, X. Practical synthesis of symmetrical thioureas and heterocyclic thiones in water. *J. Chem. Res.* **2016**, *40*, 515-518.

(16) Keri, R. S.; Patil, M. R.; Patil, S. A.; Budagumpi, S. A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry. *Eur. J. Med. Chem.* **2015**, *89*, 207-251.

(17) (a) Li, C. J. Organic reactions in aqueous media with a focus on carbon-carbon bond formations: a decade update. *Chem. Rev.* **2005**, *105*, 3095-3166. (b) Li, C. J. Organic reactions in aqueous media-with a focus on carbon-carbon bond formation. *Chem. Rev.* **1993**, *93*, 2023-2035. (c) Li, C. J. Cross-dehydrogenative coupling (CDC): exploring C-C bond formations beyond functional group transformations. *Acc. Chem. Res.* **2009**, *42*, 335-344. (d) Kobayashi, S.; Manabe, K. Development of novel lewis acid catalysts for selective organic reactions in aqueous media. *Acc. Chem. Res.* **2002**, *35*, 209-217. (e) Manabe, K.; Sun, X. M.; Kobayashi, S. Dehydration reactions in water. surfactant-type Brønsted acid-catalyzed direct esterification of carboxylic acids with alcohols in an emulsion system. *J. Am. Chem. Soc.* **2001**, *123*, 10101-10102. (f) Loh, T. P.; Li, X. R. A simple and practical synthesis of a-trifluoromethylated alcohols in water.

Tetrahedron **1999**, *55*, 5611-5622.

(18) Shah, S. T. A.; Khan, K. M.; Heinrich, A. M.; Voelter, W. An alternative approach towards the syntheses of thioethers and thioesters using CsF–Celite in acetonitrile. *Tetrahedron Lett.* **2002**, *43*, 8281-8283.

(19) Koči, J.; Klimešova, V.; Waisser, K.; Kaustova, J.; Dahse, H. M.; Mollmann, U. Heterocyclic benzazole derivatives with antimycobacterial in vitro activity. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3275-3278.

(20) Ramanatham, V. K.; Kotha, V. S. K.; Kotarkonda, R. G. Facile synthesis of 2 - (substitutedbenzylsulfanyl) - benzothiazoles and their antimicrobial activity screening. *J. Heterocycl. Chem.* **2005**, *42*, 153-156.

(21) (a) Mayer, S. F.; Kroutil, W.; Faber, K. Enzyme-initiated domino (cascade) reactions. *Chem. Soc. Rev.* **2001**, *30*, 332-339. (b) Clark, A. J. Atom transfer radical cyclisation reactions mediated by copper complexes. *Chem. Soc. Rev.* **2002**, *31*, 1-11. (c) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. Tandem reaction sequences under hydroformylation conditions: new synthetic applications of transition metal catalysis. *Chem. Rev.* **1999**, *99*, 3329-3366. (d) Denmark, S. E.; Thorarensen, A. Tandem [4+ 2]/[3+ 2] Cycloadditions of Nitroalkenes. *Chem. Rev.* **1996**, *96*, 137-166. (e) Winkler, J. D. Tandem Diels−Alder cycloadditions in organic synthesis. *Chem. Rev.* **1996**, *96*, 167-176. (f) Parsons, P. J.; Penkett, C. S.; Shell, A. J. Tandem reactions in organic synthesis: novel strategies for natural product elaboration and the development of new synthetic methodology. *Chem. Rev.* **1996**, *96*, 195-206. (g) Bunce, R. A. Recent advances in the use of tandem reactions for organic synthesis. *Tetrahedron* **1995**, *51*, 13103-13159.

(22) Murru, S.; Ghosh, H.; Sahoo, S. K.; Patel, B. K. Intra-and intermolecular C-S bond formation using a single catalytic system: first direct access to arylthiobenzothiazoles. *Org. Lett*. **2009**, *11*, 4254-4257.

(23) Shi, L.; Liu, X.; Zhang, H.; Jiang, Y.; Ma, D. Synthesis of 2-thio-substituted benzothiazoles via a domino condensation/S-arylation/heterocyclization process. *J. Org. Chem*. **2011**, *76*, 4200-4204.

(24) (a) Zeng, M. T.; Xu, W.; Liu, X.; Chang, C. Z.; Zhu, H.; Dong, Z. B. Copper-catalyzed *S*-arylation of tetraalkylthiuram disulfides by using diaryliodonium salts. *Eur. J. Org. Chem.* **2017**, 6060-6066. (b) Dong, Z. B.; Liu, X.; Bolm, C. Copper-catalyzed C(sp^2)–S coupling reactions for the synthesis of aryl dithiocarbamates with thiuram disulfide reagents. *Org. Lett.* **2017**, *19*, 5916-5919. (c) Cao, Q.; Peng, H. Y.; Cheng, Y.; Dong, Z. B. A highly efficient $CuCl_2$-catalyzed C-S coupling of aryl iodides with tetraalkylthiuram disulfides: synthesis of aryl dithiocarbamates. *Synthesis* **2018**, *50*, 1527-1534. (d) Liu, X.; Liu, M.; Xu, W.; Zeng, M. T.; Zhu, H.; Chang, C. Z.; Dong, Z. B. An environmentally benign and efficient synthesis of substituted benzothiazole-2-thiols, benzoxazole-2-thiols, and benzimidazoline-2-thiones in water. *Green Chem*. **2017**, *19*, 5591-5598. (e) Liu, M.; Zeng, M. T.; Xu, W.; Wu, L.; Dong, Z. B. Selective synthesis of 2-aminobenzoxazoles and 2-mercaptobenzoxazoles by using *O*-aminophenols as starting material. *Tetrahedron Lett*. **2017**, *58*, 4352-4356. (f) Xu, W.; Zeng, M. T.; Liu, M.; Liu, S. S.; Li, Y. S.; Dong, Z. B. Palladium-catalyzed synthesis of 2-aminobenzothiazoles through tandem reaction. *Synthesis* **2017**, *49*, 3084-3090.

(25) Enders, D.; Rembiak, A.; Liebich, J. X. Direct Organocatalytic α-sulfenylation of aldehydes and ketones with tetramethylthiuram disulfide. *Synthesis* **2011**, *2*, 281.