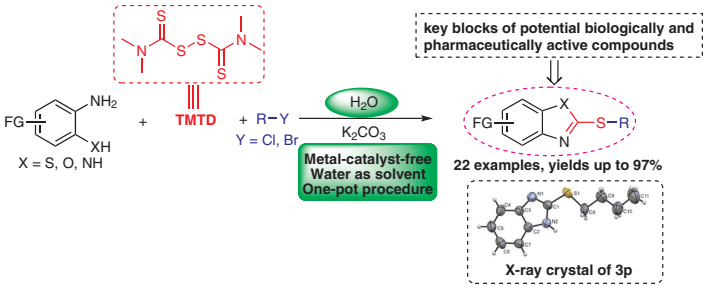
Synthesis J.-Q. Chen et al. Paper

Three-Component Synthesis of 2-Alkylthiobenzoazoles in Aqueous Media

Jin-Quan Chen[a]
Jia Guo[b,c]
Zhi-Bing Dong*[a,b,c,d]

[a] School of Chemistry and Environmental Engineering, Wuhan Institute of Technology, Wuhan 430205, P. R. of China
dzb04982@wit.edu.cn
[b] Key Laboratory of Green Chemical Process, Ministry of Education, Wuhan Institute of Technology, Wuhan 430205, P. R. of China
[c] Hubei Key Laboratory of Novel Reactor and Green Chemistry Technology, Wuhan Institute of Technology, Wuhan 430205, P. R. of China
[d] Ministry of Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules, Hubei University, Wuhan 430062, P. R. of China



Received: 19.12.2019
Accepted after revision: 14.02.2020
Published online: 16.03.2020
DOI: 10.1055/s-0039-1690854; Art ID: ss-2020-f0693-op

Abstract A highly efficient three-component protocol for the synthesis of the 2-alkylthiobenzoazoles is described. Tetramethylthiuram disulfide (TMTD) cyclized with *o*-aminothiophenols, generating the intermediate 2-mercaptobenzothiazoles, and the successive C–S coupling with halogenated alkanes afforded a series of 2-alkyl-substituted thiobenzothiazoles smoothly in a one-pot process. This procedure could also be utilized for the preparation of 2-alkyl-substituted thiobenzoxazoles and 2-alkyl-substituted thiobenzimidazoles. Inexpensive and easily available starting materials, metal catalyst-free, broad substrate scope, and water as solvent are the features of this protocol.

Key words metal-free, synthesis, thiobenzoazole, water, thiuram

Metal-free-promoted C–S bond formation has been a subject of intense study due to the importance of sulfur-substituted benzoheterocyclic compounds and their derivatives, which are popularly applied as a variety of pharmaceutical agents and bioactive natural products.[1–3] In particular, some sulfur-substituted benzoheterocyclic compounds have been reported as antiviral, antimicrobial, anticancer, antihelmintic, antifungal, antitubercular, antidiabetic, and antibacterial agents;[4] therefore, organic chemists have paid much attention to the synthesis of the 2-alkyl-substituted thiobenzoazoles, which are important units of some biologically and pharmaceutically active molecules.[5] Several examples are shown in Figure 1 to illustrate the importance of these key blocks, such as compound **1** (antituberculotic active drug), compound **2** (inhibitor of 5-lipoxygenase and cathepsin-D), timoprazole (**3**), and triclabendazole (**4**). Furthermore, some of them have efficient catalytic activity and are used in chemical reactions.[6]

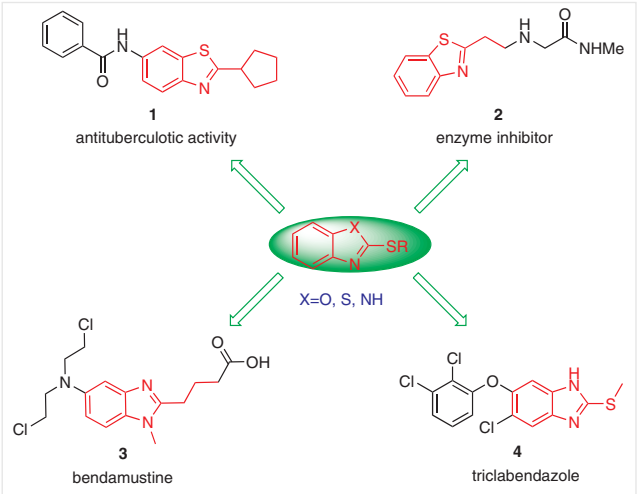
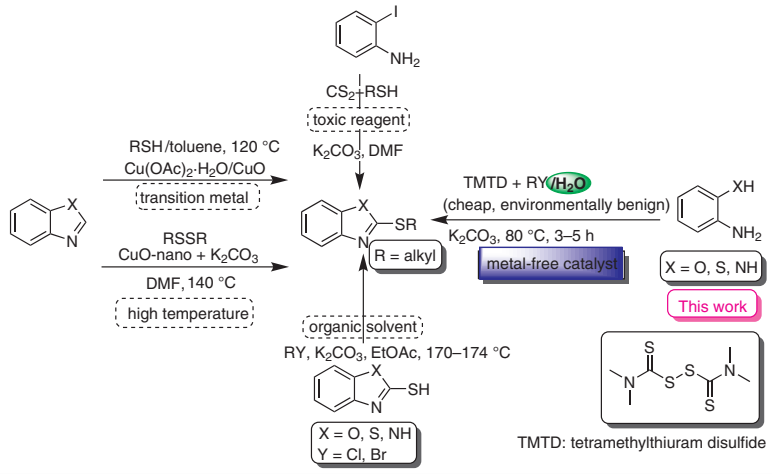


Figure 1 Representative biologically active compounds containing 2-alkyl-substituted thiobenzoazoles

There are a couple of ways to synthesize 2-alkyl-substituted thiobenzoazoles, such as the reaction of 2-aminoiodobenzenes with carbon disulfide and alkyl thiols,[5b] the reaction of benzoheterocyclic thiols with alkyl halides,[7–11] and the reaction of benzoheterocycles with alkyl thiols or dialkyl disulfides (Scheme 1).[12] However, these protocols have some drawbacks such as high temperature, use of toxic reagents or large amount of organic solvents, and the requirement of stoichiometric metal catalysts. Therefore, more convenient and environmentally friendly methods are still desirable for these important compounds.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

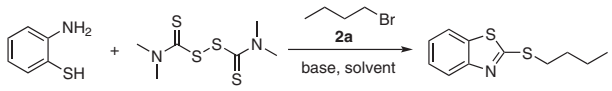


Scheme 1 Synthetic methods for 2-alkylthiobenzothiazoles, 2-alkylthiobenzoxazoles, and 2-alkylthiobenzimidazoles

Furthermore, the strategies of tandem manner have attracted a lot of attention from the organic chemists recently, since the intermediates separation is not necessary, it may thus increase the efficiency of the performance.[13–15] Thiuram reagents are cheap and commercially available organosulfur compounds with broad applications,[16] they could also be regarded as interesting reagents for the development of new synthetic transformations.[17] Recently, from the green and environmental point of view, we reported that tetramethylthiuram disulfide (TMTD) was a very useful sulfur reagent for organic synthesis.[18] As part of our efforts in organosulfur chemistry and our progress in metal-free synthesis,[19] here we would like to demonstrate a convenient and efficient protocol for the synthesis of 2-alkyl-substituted thiobenzoxazoles in a one-pot manner. The further survey on alkane halides (this work) could illustrate its good substrate adaptability, providing an easy, green, and high-efficient way to establish molecular libraries for the pharmaceutical industry. Thus, 2-aminophenols, 2-aminothiophenols, and 1,2-phenylenediamines react with TMTD by cyclization under metal-free conditions in water giving mercaptobenzoheterocycles, and the latter C–S bond formation with alkyl halides could afford the final products smoothly (Scheme 1).

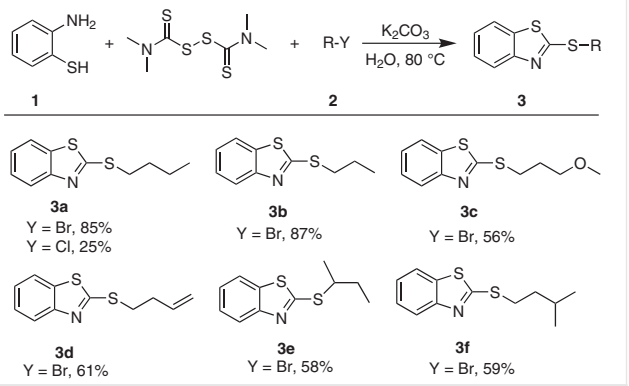
The model reaction was carried out by using 2-aminothiophenol (**1a**), TMTD, and 1-bromobutane (**2a**) as starting materials. 2-Aminothiophenol was mixed with TMTD in water and heated at 120 °C for 2–3 hours, base and 1-bromobutane were then added to this mixture before it was heated again. By varying the species of the base, the base loading, substrate ratio, reaction temperature, and solvents, the reaction conditions were optimized, and the results are layed out in Table 1. First, the effects of several bases, such as K_2CO_3, Na_2CO_3, KOH, NaOH, and $NaHCO_3$ on the reaction were tested (Table 1, entries 1–5), and the results showed that K_2CO_3 was the most suitable one, which gave the prod-

Table 1 Optimization of the Reaction Conditions[a]



Entry	Base (equiv)	Solvent	Temp (°C)[b]	Ratio[c]	Yield(%)[d]
1	K_2CO_3 (2.0)	H_2O	100	1:0.6:2	70
2	Na_2CO_3 (2.0)	H_2O	100	1:0.6:2	41
3	KOH (2.0)	H_2O	100	1:0.6:2	61
4	NaOH (2.0)	H_2O	100	1:0.6:2	63
5	$NaHCO_3$ (2.0)	H_2O	100	1:0.6:2	30
6	K_2CO_3 (1.0)	H_2O	100	1:0.6:2	43
7	K_2CO_3 (3.0)	H_2O	100	1:0.6:2	59
8	K_2CO_3 (2.0)	H_2O	100	1:0.6:1	48
9	K_2CO_3 (2.0)	H_2O	100	1:0.6:3	68
10	K_2CO_3 (2.0)	H_2O	120	1:0.6:2	45
11	**K_2CO_3 (2.0)**	**H_2O**	**80**	**1:0.6:2**	**85**
12	K_2CO_3 (2.0)	H_2O	60	1:0.6:2	68
13	K_2CO_3 (2.0)	DMF	80	1:0.6:2	79
14	K_2CO_3 (2.0)	DMSO	80	1:0.6:2	71
15	K_2CO_3 (2.0)	Toluene	80	1:0.6:2	N.R.
16	K_2CO_3 (2.0)	CH_2Cl_2	80	1:0.6:2	22

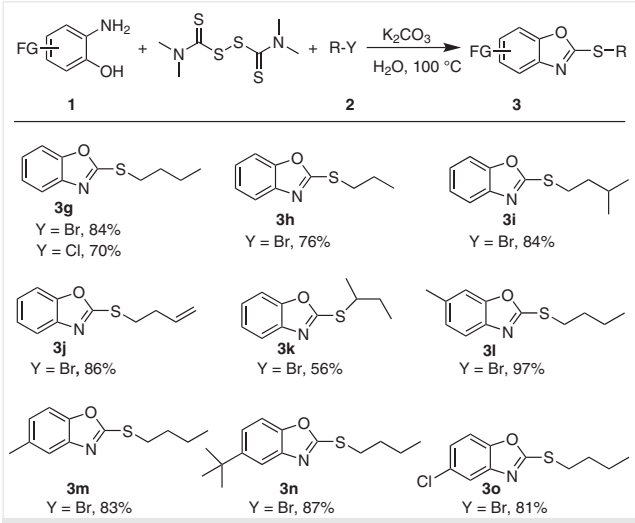
[a] Reaction conditions: **1a** (1.0 mmol), TMTD (0.6 mmol), **2a** (1.0–3.0 mmol), base (1–3 equiv), solvent (2 mL); the mixture of **1a** and TMTD was stirred at 120 °C for 2–3 h, then a mixture of base and **2a** was added subsequently.
[b] The temperature for the second step.
[c] Ratio of **1a**/TMTD/**2a**.
[d] Isolated yield based on **1a** after column chromatography. N.R. = no reaction.



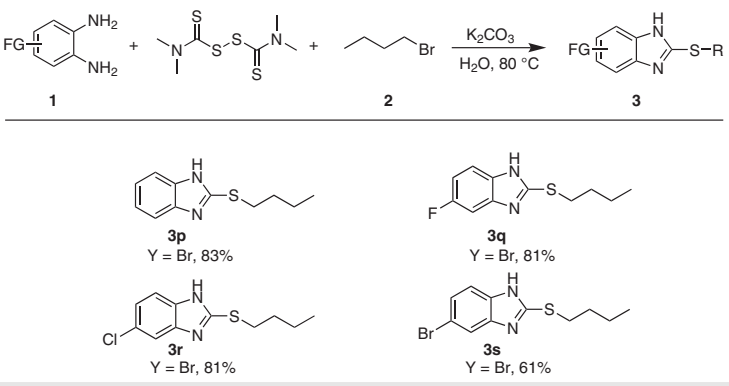
Scheme 2 Synthesis of 2-(alkylthio)benzo[*d*]thiazoles starting from 2-aminothiophenol, TMTD, and alkyl halides. *Reagents and conditions*: A mixture of 2-aminothiophenol (1.0 mmol) and TMTD (0.6 mmol) in H_2O (2.0 mL) was stirred at 120 °C for 2–3 h, then K_2CO_3 (2.0 mmol) and alkyl halide (2.0 mmol) were added to the reaction mixture, and the mixture was stirred at 80 °C for 3–5 h.

uct in 70% yield (entry 1). Next, the amount of K_2CO_3 was selected (entries 1, 6, 7), and 2.0 equivalents of K_2CO_3 were found to be the optimal loading amount. Then, the investigation on substrate ratio (**1a**/TMTD/**2a**) was performed (entries 1, 8, 9), and it was shown that a ratio of **1a**/TMTD/**2a** = 1:0.6:2 was the best. In addition, reaction temperature screening (for the second step) was examined (entries 1, 10–12), and 80 °C was found to be the most suitable one. The subsequent control experiments showed that the most suitable temperature to give 2-alkylthiobenzoxazole was 100 °C and the best reaction temperature to give 2-alkylthiobenzimidazole was 80 °C. Finally, various solvents such as H_2O, DMF, DMSO, toluene, and CH_2Cl_2 were tested (entries 11, 13–16), and H_2O was found to be the best solvent for this reaction. The best reaction conditions are shown in entry 11 of Table 1.

Having the optimized reaction conditions in hand, we began to survey the substrate scope. First, the reactivity of alkyl halides in the presence of *2*-aminothiophenol was examined (Scheme 2). The reaction proceeded smoothly and we could obtain the intended tandem reaction (cyclization, then C–S formation) products in moderate to good yields. Generally, 2-aminothiophenol and TMTD reacted better with alkyl bromides than the ones with alkyl chloride. 1-Bromobutane reacted with 2-aminothiophenol and TMTD, furnishing the product **3a** in 85% yield, while 1-chlorobutane reacted with the corresponding starting material giving the product **3a** in 25% yield. There is obvious difference in the reactivity between primary alkyl halogen and



Scheme 3 Synthesis of 2-(alkylthio)benzo[*d*]oxazoles starting from 2-aminophenols, TMTD and alkyl halides. *Reagents and conditions*: The mixture of 2-aminophenol (1.0 mmol) and TMTD (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 alkyl halide (2.0 mmol) were added to the reaction, and the mixture was stirred at 100 °C for 3–5 h.



Scheme 4 Synthesis of 2-(alkylthio)-1*H*-benzo[*d*]imidazole starting from 2-arylenediamines, TMTD, and 1-bromobutane. *Reagents and conditions*: The mixture of 2-arylenediamines (1.0 mmol) and TMTD (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 1-bromobutane (2.0 mmol) were added to the reaction, and the mixture was stirred at 80 °C for 3–5 h.

secondary alkyl halogen in this reaction. 2-Bromobutane gave the products **3e** in 58% yield while 1-bromopropane furnished the product **3b** in 87% yield, and 1-bromo-3-methylbutane gave the product **3f** in 59% yield. To our delight, the methoxy- and alkenyl-substituted alkyl chain were all suitable for the transformation under the standard reaction conditions, and gave the corresponding products **3c** and **3d** in 56–61% yields.

Next, we checked the reactivity of the alkyl halides in the presence of various 2-aminophenols and 2-phenylenediamines (Scheme 3 and Scheme 4). Likewise, the tandem reaction proceeded smoothly and the intended products were generated in good to excellent yields. The results in Schemes 2–4 revealed that the protocol featured good substrate compatibility, providing a convenient and easy way for preparation of potential drug molecules in pharmaceutical industry. To further confirm the structure of the desired product, the product **3p** was characterized by X-ray crystallography (Figure 2).[20]

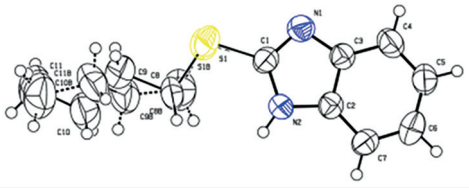


Figure 2 X-ray crystal structure of **3p**[20]

According to the above results and our previous work on C–S formation,[18] we propose a possible pathway as shown in Scheme 5. TMTD **A** reacts with aniline **B** to generate intermediate thiourea **C**, the XH (X = O, S, NH) undergoes intramolecular nucleophilic addition giving intermediate **D**. The subsequent intramolecular elimination allows **D** to give the intermediate **E**, which is in dynamic equilibrium with the mercaptobenzoheterocycle **F**. Benzoheterocycle **F** processes the latter S_N2 pathway with alkyl halide to furnish the final product **G** easily.

In summary, a simple, efficient, and one-pot protocol for the preparation of 2-alkylthiobenzoazoles in water was developed. By using 2-aminothiophenols, 2-aminophenols, and 1,2-phenylenediamines as starting materials, the mercaptobenzoheterocycles were synthesized by cyclization by reacting with TMTD, and the latter C–S coupling generated the final products in good yields. The features of this protocol are metal catalyst-free, easy performance, wide substrates scope, and water as solvent, showing its practical and useful value in organic synthesis. Further development and related applications for this method are under investigation in our lab.

Flash column chromatography was operated on silica gel with PE/EtOAc as the eluent. TLC was adopted and visualized under UV light. The RY-1G instrument was used to determine melting points of target compounds. The HRMS (high-resolution mass spectra) was recorded on a Finnigan MAT 95Q mass instrument (ESI). A Bruker AM400 NMR instrument was operated in $CDCl_3$ to record the NMR spectra.

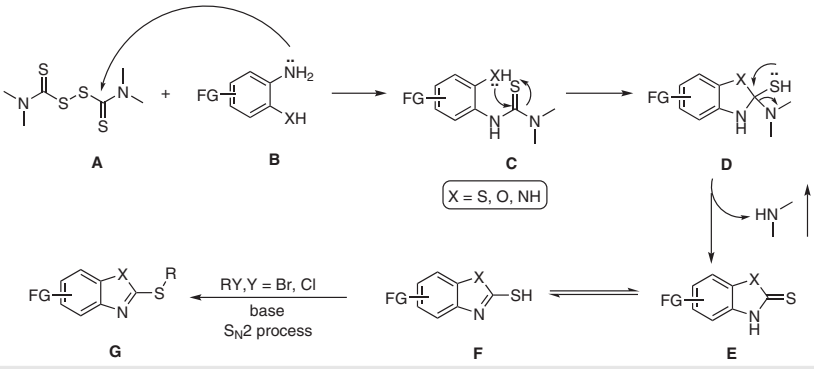
2-(Butylthio)benzo[*d*]thiazole (3a); Typical Procedure

A mixture of 2-aminobenzenethiol (**1a**; 1.0 mmol) and TMTD (0.6 mmol) in H_2O (2.0 mL) was heated at 120 °C for 2–3 h, then K_2CO_3 (2.0 mmol) and 1-bromobutane (**2a**; 2.0 mmol) were added to the reaction mixture. The mixture was stirred at 80 °C and the reaction was monitored by TLC (about 5 h). The reaction was then quenched with aq NH_4Cl, and extracted with EtOAc. The combined extracts were dried (anhyd Na_2SO_4) and concentrated under vacuum. The crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3a** as a yellow oil; yield: 190 mg (85%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.76 (d, *J* = 8.0 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 3.23 (t, *J* = 8.0 Hz, 2 H), 1.72–1.65 (m, 2 H), 1.44–1.34 (m, 2 H), 0.85 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 152.3, 134.0, 124.9, 123.0, 120.3, 119.8, 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: 224.0564.



Scheme 5 Plausible reaction mechanism

2-(Propylthio)benzo[*d*]thiazole (3b)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3b** as a brown oil; yield: 181 mg (87%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.74 (d, *J* = 8.0 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 3.18 (t, *J* = 8.0 Hz, 2 H), 1.76–1.65 (m, 2 H), 0.94 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 152.2, 134.0, 124.8, 123.0, 120.3, 119.8, 34.4, 21.6, 12.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{12}NS_2$: 210.0406; found: 210.0409.

2-[(3-Methoxypropyl)thio]benzo[*d*]thiazole (3c)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 50:1) to give **3c** as a pale yellow oil; yield: 135 mg (56%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.75 (d, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.28 (t, *J* = 8.0 Hz, 1 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 3.40 (t, *J* = 8.0 Hz, 2 H), 3.31 (t, *J* = 8.0 Hz, 2 H), 3.23 (s, 3 H), 2.02–1.95 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 152.2, 134.1, 124.9, 123.0, 120.3, 119.8, 69.6, 57.5, 29.3, 28.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NOS_2$: 240.0511; found: 240.0515.

2-(But-3-en-1-ylthio)benzo[*d*]thiazole (3d)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3d** as a yellow oil; yield: 135 mg (61%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.76 (d, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 7.16 (t, *J* = 8.0 Hz, 1 H), 5.82–5.72 (m, 1 H), 5.06–4.98 (m, 2 H), 3.32 (t, *J* = 8.0 Hz, 2 H), 2.49–2.44 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 152.2, 134.6, 134.1, 124.9, 123.0, 120.4, 119.8, 115.8, 32.2, 31.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NS_2$: 220.0406; found: 220.0409.

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

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3e** as a brown oil; yield: 130 mg (58%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.77 (d, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.28 (t, *J* = 8.0 Hz, 1 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 3.87–3.79 (m, 1 H), 1.76–1.59 (m, 2 H), 1.39 (d, *J* = 4.0 Hz, 3 H), 0.95 (d, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 152.3, 134.2, 124.8, 123.1, 120.4, 119.8, 44.8, 28.6, 19.8, 10.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NS_2$: 224.0562; found: 224.0566.

2-(Isopentylthio)benzo[*d*]thiazole (3f)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3f** as a brown oil; yield: 139 mg (59%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.77 (d, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 7.16 (t, *J* = 8.0 Hz, 1 H), 3.24 (t, *J* = 8.0 Hz, 2 H), 1.72–1.57 (m, 3 H), 0.86 (d, *J* = 8.0 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 152.3, 134.1, 124.9, 123.0, 120.3, 119.8, 36.9, 30.6, 26.4, 21.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NS_2$: 238.0719; found: 238.0714.

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

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 20:1) to give **3g** as a yellow oil; yield: 174 mg (84%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.49 (d, *J* = 4.0 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.16–7.07 (m, 2 H), 3.19 (t, *J* = 8.0 Hz, 2 H), 1.73–1.65 (m, 2 H), 1.43–1.34 (m, 2 H), 0.85 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 150.7, 140.9, 123.1, 122.6, 117.2, 108.7, 30.9, 30.2, 20.7, 12.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NOS$: 208.0791; found: 208.0795.

2-(Propylthio)benzo[*d*]oxazole (3h)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3h** as a pale yellow oil; yield: 146 mg (76%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.52 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.21–7.13 (m, 2 H), 3.21 (t, *J* = 8.0 Hz, 2 H), 1.84–1.71 (m, 2 H), 1.01 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 150.7, 140.9, 123.1, 122.7, 117.2, 108.7, 33.1, 21.7, 12.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{12}NOS$: 194.0634; found: 194.0638.

2-(Isopentylthio)benzo[*d*]oxazole (3i)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3i** as a palm red oil; yield: 186 mg (84%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.49 (d, *J* = 4.0 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.16–7.70 (m, 2 H), 3.20 (t, *J* = 8.0 Hz, 2 H), 1.71–1.56 (m, 3 H), 0.85 (d, *J* = 8.0 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 150.7, 140.9, 123.1, 122.6, 117.2, 108.7, 36.9, 29.3, 26.3, 21.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NOS$: 222.0947; found: 222.0945.

2-(But-3-en-1-ylthio)benzo[*d*]oxazole (3j)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3j** as a yellow oil; yield: 177 mg (86%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.49 (d, *J* = 8.0 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.17–7.08 (m, 2 H), 5.81–5.70 (m, 1 H), 5.06–4.98 (m, 2 H), 3.25 (t, *J* = 8.0 Hz, 2 H), 2.50–2.45 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 150.7, 140.9, 134.3, 123.1, 122.7, 117.2, 116.0, 108.7, 32.2, 30.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NOS$: 206.0634; found: 206.0636.

2-(*sec*-Butylthio)benzo[*d*]oxazole (3k)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3k** as a yellow oil; yield: 116 mg (56%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.50 (d, *J* = 8.0 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.18–7.09 (m, 2 H), 3.84–3.75 (m, 1 H), 1.79–1.62 (m, 2 H), 1.42 (d, *J* = 8.0 Hz, 3 H), 0.96 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 150.5, 140.9, 123.1, 122.7, 117.3, 108.7, 43.8, 28.5, 20.0, 10.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NOS$: 208.0791; found: 208.0798.

2-(Butylthio)-6-methylbenzo[*d*]oxazole (3l)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3l** as a yellow oil; yield: 233 mg (97%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.34 (d, *J* = 8.0 Hz, 1 H), 7.09 (s, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 3.17 (t, *J* = 8.0 Hz, 2 H), 2.31 (s, 3 H), 1.72–1.64 (m, 2 H), 1.43–1.34 (m, 2 H), 0.85 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 151.0, 138.7, 132.9, 124.1, 116.6, 109.0, 30.9, 30.2, 20.7, 20.5, 12.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NOS$: 222.0947; found: 222.0945.

2-(Butylthio)-5-methylbenzo[*d*]oxazole (3m)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3m** as a palm red oil; yield: 222 mg (83%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.28 (s, 1 H), 7.17 (d, *J* = 8.0 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 3.19 (t, *J* = 8.0 Hz, 2 H), 2.32 (s, 3 H), 1.73–1.65 (m, 2 H), 1.44–1.34 (m, 2 H), 0.85 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 148.9, 141.1, 132.8, 123.5, 117.3, 108.0, 30.9, 30.2, 20.7, 20.3, 12.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NOS$: 222.0947; found: 222.0945.

5-(*tert*-Butyl)-2-(butylthio)benzo[*d*]oxazole (3n)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3n** as a brown oil; yield: 277 mg (87%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.54 (s, 1 H), 7.23–7.15 (m, 2 H), 3.19 (t, *J* = 8.0 Hz, 2 H), 1.74–1.66 (m, 2 H), 1.44–1.35 (m, 2 H), 1.25 (s, 9 H), 0.85 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 148.7, 146.6, 140.8, 120.1, 113.9, 107.8, 33.8, 30.9, 30.7, 30.2, 20.7, 12.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}NOS$: 264.1417; found: 264.1412.

2-(Butylthio)-5-chlorobenzo[*d*]oxazole (3o)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3o** as a yellow oil; yield: 196 mg (81%).

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.45 (s, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 7.07 (d, *J* = 8.0 Hz, 1 H), 3.19 (t, *J* = 8.0 Hz, 2 H), 1.73–1.66 (m, 2 H), 1.44–1.35 (m, 2 H), 0.86 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 149.2, 142.0, 128.6, 122.7, 117.3, 109.2, 31.0, 30.1, 20.7, 12.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}ClNOS$: 242.0401; found: 242.0403.

2-(Butylthio)-1*H*-benzo[*d*]imidazole (3p)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 10:1) to give **3p** as a white solid; yield: 172 mg (83%); mp 133–135 °C.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 10.46 (s, 1 H), 7.46–7.44 (m, 2 H), 7.11–7.09 (m, 2 H), 3.22 (t, *J* = 8.0 Hz, 2 H), 1.65–1.58 (m, 2 H), 1.31–1.22 (m, 2 H), 0.73 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 138.6, 121.1, 113.0, 31.4, 30.5, 20.7, 12.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}N_2S$: 207.0950; found: 207.0955.

2-(Butylthio)-5-fluoro-1*H*-benzo[*d*]imidazole (3q)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 3:1) to give **3q** as a yellow solid; yield: 181 mg (81%); mp 99–101 °C.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 10.32 (s, 1 H), 7.37–7.34 (m, 1 H), 7.17–7.12 (m, 1 H), 6.89–6.84 (m, 1 H), 3.20 (t, *J* = 8.0 Hz, 2 H), 1.66–1.58 (m, 2 H), 1.32–1.23 (m, 2 H), 0.75 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3 (d, *J* = 237.0 Hz), 151.2, 138.4 (d, *J* = 13.0 Hz), 134.8, 113.3 (d, *J* = 10.0 Hz), 109.2 (d, *J* = 25.0 Hz), 99.4 (d, *J* = 26.0 Hz), 31.5, 30.5, 20.7, 12.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}FN_2S$: 225.0856; found: 225.0851.

2-(Butylthio)-5-chloro-1*H*-benzo[*d*]imidazole (3r)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 3:1) to give **3r** as a yellow solid; 194 mg (81%); mp 120–122 °C.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.43 (d, *J* = 4.0 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.10–7.07 (m, 1 H), 3.23 (t, *J* = 8.0 Hz, 2 H), 1.68–1.61 (m, 2 H), 1.37–1.28 (m, 2 H), 0.80 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.3, 138.8, 136.8, 126.9, 121.7, 113.6, 112.8, 31.4, 30.5, 20.7, 12.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}ClN_2S$: 241.0561; found: 241.0568.

5-Bromo-2-(butylthio)-1*H*-benzo[*d*]imidazole (3s)

Following the typical procedure, the crude material was purified by column chromatography on silica gel (PE/EtOAc 3:1) to give **3s** as a brown solid; yield: 174 mg (61%); mp 110–112 °C.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 9.23 (s, 1 H), 7.59 (s, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.20 (t, *J* = 8.0 Hz, 1 H), 3.21 (t, *J* = 8.0 Hz, 2 H), 1.67–1.59 (m, 2 H), 1.34–1.25 (m, 2 H), 0.77 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 139.4, 137.2, 124.3, 115.8, 114.3, 114.0, 31.4, 30.5, 20.7, 12.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}BrN_2S$: 285.0056; found: 285.0059.

Funding Information

The financial support from Hubei Key Laboratory of Radiation Chemistry and Functional Materials, Hubei University of Science & Technology (2019-20KZ01), Ministry of Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules, Hubei University (KLSAOFM1810), Science and Technology Department of Hubei Province (2019CFB596), Key Laboratory of Hubei Province for

Coal Conversion and New Carbon Materials (WKDM202003) are all greatly appreciated. J.-Q.C. thanks the support of Postgraduate Innovation Foundation from Wuhan Institute of Technology (CX2019170).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690854.

References

(1) (a) Yu, Y. F.; Li, Z. N.; Jiang, L. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012**, *187*, 632. (b) Liang, G. G.; Liu, M. C.; Chen, J. X.; Ding, J. C.; Gao, W. X.; Wu, H. Y. *Chin. J. Chem.* **2012**, *30*, 1611. (c) Dan, W. X.; Deng, H. J.; Chen, J. X.; Liu, M. C.; Ding, J. C.; Wu, H. Y. *Tetrahedron* **2010**, *66*, 7384. (d) Guo, W. X.; Chen, J. X.; Wu, D. Z.; Ding, J. C.; Wu, H. Y. *Tetrahedron* **2009**, *65*, 5240. (e) Liu, M. C.; Lin, S. M.; Ding, J. C.; Gao, W. X.; Wu, H. Y.; Chen, J. X. *Tetrahedron* **2013**, *69*, 2283.

(2) He, M. C.; Yan, Z. H.; Zhu, F. Y.; Lin, S. *J. Org. Chem.* **2018**, *83*, 15438.

(3) (a) Deligeorgiev, T.; Kaloyanova, S.; Lesev, N.; Vaquero, J. J. *Ultrason. Sonochem.* **2010**, *17*, 783. (b) Ranjit, S.; Lee, R.; Heryadi, D.; Shen, C.; Wu, J. E.; Zhang, P. F.; Huang, K. W.; Liu, X. G. *J. Org. Chem.* **2011**, *76*, 8999. (c) Dai, C.; Xu, Z. Q.; Huang, F.; Yu, Z. K.; Gao, Y. F. *J. Org. Chem.* **2012**, *77*, 4414. (d) Yang, X. L.; Xu, Y. L.; Chen, J. X.; Ding, J. C.; Wu, H. Y.; Su, W. K. *J. Chem. Res.* **2009**, *11*, 682.

(4) (a) Suresh, C. H.; Rao, J. V.; Jayaveera, K. N.; Subudhi, S. K. *Int. Res. J. Pharm.* **2011**, *2*, 257. (b) Singh, M.; Singh, S. K.; Gangwar, M.; Nath, G.; Singh, S. K. *RSC Adv.* **2014**, *4*, 19013. (c) Rao, A. J.; Rao, P. V.; Rao, V. K.; Mohan, C.; Raju, C. N.; Reddy, C. S. *Bull. Korean Chem. Soc.* **2010**, *31*, 1863. (d) Singh, S. P.; Segal, S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1988**, *27*, 941. (e) Palmer, P. J.; Trigg, R. B.; Warrington, J. V. *J. Med. Chem.* **1971**, *14*, 248. (f) Pattan, S. R.; Suresh, C.; Pujar, V. D.; Reddy, V. V. K.; Rasal, V. P.; Koti, B. C. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2005**, *44*, 2404. (g) Huang, S. T.; Hsei, I. J.; Chen, C. *Bioorg. Med. Chem.* **2006**, *14*, 6106. (h) Akhtar, T.; Hameed, S.; Al-Masoudi, N. A.; Loddo, R.; Colla, P. *Acta Pharm.* **2008**, *58*, 135. (i) Yang, X. L.; Xu, C. M.; Lin, S. M.; Chen, J. X.; Ding, J. C.; Wu, H. Y.; Su, W. K. *J. Braz. Chem. Soc.* **2010**, *21*, 37. (j) Hu, K.; Qi, L. J.; Yu, S. L.; Cheng, T. X.; Wang, X. D.; Li, Z. J.; Xia, Y. Z.; Chen, J. X.; Wu, H. Y. *Green Chem.* **2017**, *19*, 1740. (k) Yu, S. L.; Hu, K.; Gong, J. L.; Qi, L. J.; Zhu, J. H.; Zhang, Y. T.; Cheng, T. X.; Chen, J. X. *Org. Biomol. Chem.* **2017**, *15*, 4300.

(5) (a) Ali, M.; Ali, S.; Khan, M.; Rashid, U.; Ahmad, M.; Khan, A.; Al-Harrasi, A.; Ullah, F.; Latif, A. *Bioorg. Chem.* **2018**, *80*, 472. (b) Shi, L.; Liu, X. Q.; Zhang, H.; Jiang, Y. W.; Ma, D. *J. Org. Chem.* **2011**, *76*, 4200.

(6) Zhang, H. F.; Liu, D. M.; Kang, T. T.; Wang, Y.; Zhang, X. X.; Zhu, X. B. *Chin. J. Org. Chem.* **2016**, *36*, 1104.

(7) Zhang, T. H.; He, H. X.; Du, J. L.; He, Z. J.; Yao, S. *Molecules* **2018**, *23*, 2011.

(8) Gao, M. C.; Wang, M.; Zheng, Q. H. *Appl. Radiat. Isotopes* **2008**, *66*, 506.

(9) Dalal, D. S.; Pawar, N. S.; Mahulikar, P. P. *Org. Prep. Proced. Int.* **2005**, *37*, 539.

(10) Li, Y. W.; Gu, G. B.; Liu, H. Y.; Sung, H. Y.; Williams, L. D.; Chang, C. K. *Molecules* **2005**, *10*, 912.

(11) (a) Sih, J. C.; Graber, D. R. *J. Org. Chem.* **1983**, *48*, 3842. (b) Klimesova, V.; Koci, J.; Pour, M.; Stachel, J.; Waisser, K.; Kaustova, J. *Eur. J. Med. Chem.* **2002**, *37*, 409. (c) Hu, Y.; Chen, Z. C.; Le, Z. G.; Zheng, Q. G. *Synth. Commun.* **2004**, *34*, 2039. (d) Mésangeau, C.; Narayanan, S.; Green, A. M.; Shaikh, J.; Kaushal, N.; Viard, E.; Xu, Y. T.; Fishback, J. A.; Poupaert, J. H.; Matsumoto, R. R.; McCurdy, C. R. *J. Med. Chem.* **2008**, *51*, 1482.

(12) (a) Rosario, A. R.; Casola, K. K.; Oliveira, C. E. S.; Zeni, G. *Adv. Synth. Catal.* **2013**, *355*, 2960. (b) Rafique, J.; Saba, S.; Frizon, T. E. A.; Braga, A. L. *ChemistrySelect* **2018**, *3*, 12387. (c) Zhou, A. X.; Liu, X. Y.; Yang, K.; Zhao, S. C.; Liang, Y. M. *Org. Biomol. Chem.* **2011**, *9*, 5456.

(13) (a) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (c) Mayer, S. F.; Kroutil, W.; Faber, K. *Chem. Soc. Rev.* **2001**, *30*, 332. (d) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (e) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329. (f) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1. (g) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.

(14) Murru, S.; Ghosh, H.; Sahoo, S. K.; Patel, B. K. *Org. Lett.* **2009**, *11*, 4254.

(15) Shi, L.; Liu, X.; Zhang, H.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2011**, *76*, 4200.

(16) Enders, D.; Rembiak, A.; Liebich, J. X. *Synthesis* **2011**, 281.

(17) (a) Zeng, M. T.; Xu, W.; Liu, M.; Liu, X.; Chang, C. Z.; Zhu, H.; Dong, Z. B. *Synth. Commun.* **2017**, *47*, 1434. (b) Dong, Z. B.; Wang, M.; Zhu, H.; Liu, X.; Chang, C. Z. *Synthesis* **2017**, *49*, 5258.

(18) Liu, X.; Liu, M.; Xu, W.; Zeng, M. T.; Zhu, H.; Chang, C. Z.; Dong, Z. B. *Green Chem.* **2017**, *19*, 5591.

(19) (a) Cao, Q.; Peng, Y. H.; Cheng, Y.; Dong, Z. B. *Synthesis* **2018**, *50*, 1527. (b) Zhang, S. B.; Liu, X.; Gao, M. Y.; Dong, Z. B. *J. Org. Chem.* **2018**, *83*, 14933. (c) Dong, Z. B.; Liu, X.; Bolm, C. *Org. Lett.* **2017**, *19*, 5916. (d) Xu, W.; Zeng, M. T.; Liu, M.; Liu, S. S.; Li, Y. S.; Dong, Z. B. *Synthesis* **2017**, *49*, 3084. (e) Zeng, M. T.; Xu, W.; Liu, X.; Chang, C. Z.; Zhu, H.; Dong, Z. B. *Eur. J. Org. Chem.* **2017**, 6060. (f) Liu, M.; Zeng, M. T.; Xu, W.; Wu, L.; Dong, Z. B. *Tetrahedron Lett.* **2017**, *58*, 4352.

(20) CCDC 1971891 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.