JOC The Journal of Organic Chemistry

Article

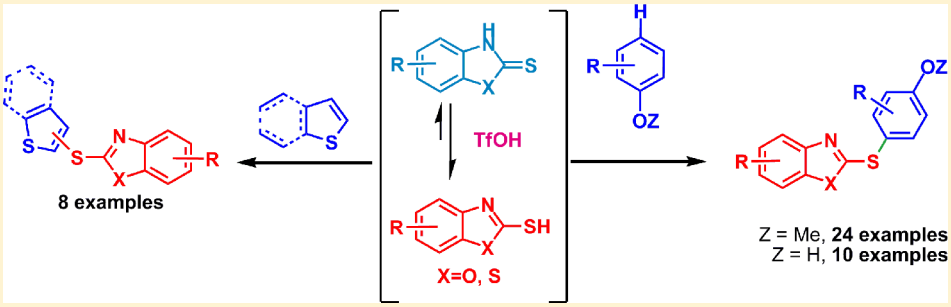
pubs.acs.org/joc

Regioselective Thiolation of Arenes and Heteroarenes: C−H Functionalization Strategy for C−S Bond Formation

Begur Vasanthkumar Varun and Kandikere Ramaiah Prabhu*

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, Karnataka, India

Supporting Information



ABSTRACT: A facile transition-metal-free oxidative cross-dehydrogenative coupling reaction involving selective formation of a C−S bond leading to the synthesis of arylthiobenzoxazoles, heteroarylthiobenzoxazoles, and arylthiobenzothiazoles has been described. This highly regioselective C−H functionalization reaction with electron-rich aromatic systems including heteroaromatics is achieved by reversing the reactivity of sulfur in the presence of a suitable oxidant and strong acid.

INTRODUCTION

The sulfur-containing organic compounds are of great significance in chemistry and biology.[1] Thioethers of benzazoles (benzoxazoles and benzothiazoles) have been important targets due to their biological activities.[2] They are extensively useful as anticancer agents, enzyme inhibitors, antagonizing agents, antituberculosis agents, and fungicides (Figure 1).[3] Particularly, the 3,4,5-trimethoxyphenyl thioether of benzoxazole shows anti-breast-cancer activity.[3j] Generally, thioethers of benzothiazoles are synthesized using 2-mercaptobenzothiazoles in reactions with aryl halides,[4a−e] aryl boronic acids,[4f] or alcohols.[4g,h] It is also well-known that direct C−H thiolation of benzazoles can be carried out with thiols[5a−c] and disulfides[5d,e] using metal catalysts such as Cu or Rh. Similarly, disulfides can also be cleaved and coupled with electron-rich arenes under suitable conditions.[5f,g] Furthermore, catechols are known to undergo oxidation to their corresponding quinones under electrochemical conditions,[6] and these quinones are coupled with 2-mercaptobenzoxazoles to give catechol thioethers, which exhibit antibacterial and antioxidant properties[6] (Scheme 1). 2-Thio-substituted benzothiazoles are also synthesized by a domino reaction using copper catalysts.[7]

C−H functionalization is one of the thrust areas which is rapidly developing as it offers an efficient, economical, and environmentally benign strategy for functionalization of unfunctionalized organic molecules.[8] Although the C−H functionalization strategy is attractive, it is challenging to achieve selective functionalization as C−H bonds are ubiquitous and activation of inert C−H bonds is a demanding task.[9] However, the C−H bond functionalization strategy using CDC (cross-dehydrogenative coupling) reactions for the formation of a C−S bond is a relatively less explored area, because thiols and sulfur compounds are known to undergo oxidation during transformations and often poison the metal catalysts by binding to them irreversibly.[10] Therefore, CDC reactions to generate C−S bonds in the absence of both thiols and metal catalysts would be a practically viable and useful strategy. In continuation of our investigation on C−H functionalization,[11] we conceptualized a strategy by using thiones as masked thiols to form C−S bonds by employing a suitable oxidant and reaction conditions. Benzoxazole-2-thione **1a** exists in equilibrium with its thiol form in the presence of a strong acid (Scheme 1), in which the sulfur atom behaves as a good nucleophile.[12] We anticipated that it may be possible to reverse the reactivity of sulfur in the presence of an additive/oxidant and couple it with a suitable nucleophile/pronucleophile.

RESULTS AND DISCUSSION

To test the above hypothesis, we began our investigation using 5-methylbenz[*d*]oxazole-2(3*H*)-thione (**1a**) and anisole (**2a**) in the presence of a variety of oxidants as well as strong acids. Reactions of **1a** and **2a** at room temperature (with TFA) as well as at 60 °C (with TFA, $MeSO_3H$, PTSA, or $HClO_4$) in CH_3CN were not successful (entries 1−5, Table 1). However, the reaction of **1a** with **2a** in the presence of $K_2S_2O_8$ and TfOH in CH_3CN at higher temperatures (60 and 80 °C) furnished the product **3a** in good yields (2 h, 76% and 74%, respectively, entries 6 and 7). A reaction of **1a** and **2a** at room temperature in CH_3CN

Received: August 4, 2014
Published: September 17, 2014

dx.doi.org/10.1021/jo501793q | *J. Org. Chem.* 2014, 79, 9655−9668

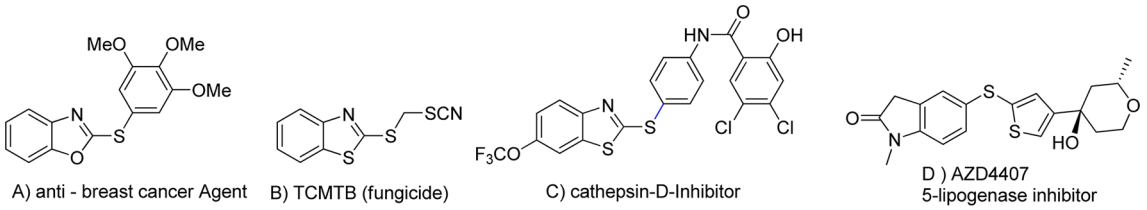


Figure 1. Examples of pharmaceutically active azole derivatives.

Scheme 1

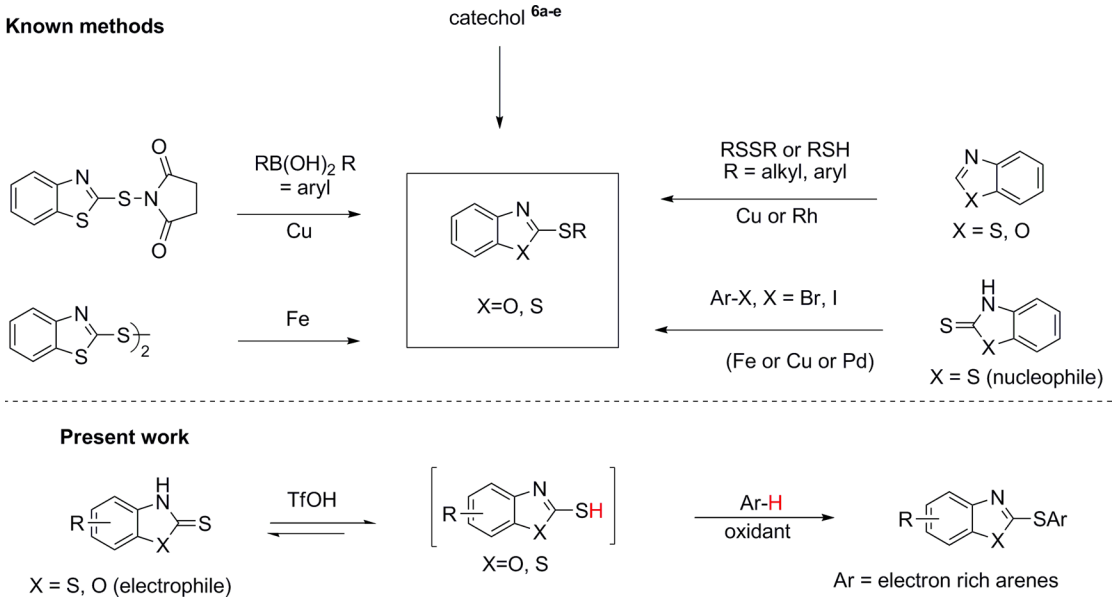
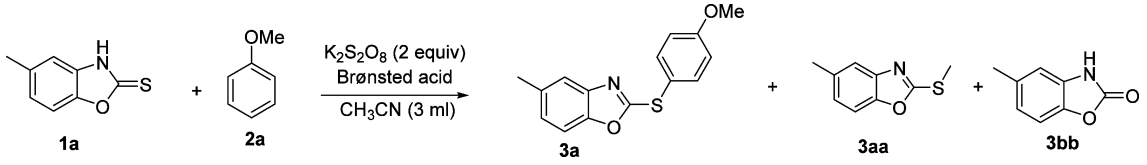


Table 1. Screening Studies[a]

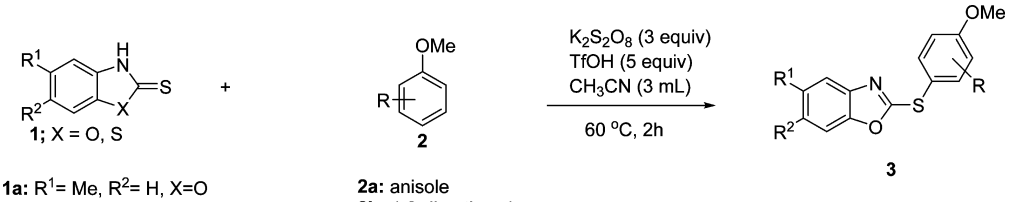


entry	2a (equiv)	oxidant (equiv)	acid (equiv)	temp (°C)	solvent	time (h)	yield (%)[b] 3a	3aa	3bb
1	5	$K_2S_2O_8$ (2.0)	TFA (5)	RT	CH_3CN	24	nd	nd	nd
2	5	$K_2S_2O_8$ (2.0)	TFA (5)	60	CH_3CN	24	nd	trace	nd
3	5	$K_2S_2O_8$ (2.0)	$MeSO_3H$ (5)	60	CH_3CN	2	nd	trace	nd
4[c]	5	$K_2S_2O_8$ (2.0)	PTSA·H_2O (5)	60	CH_3CN	2	nd	nd	nd
5	5	$K_2S_2O_8$ (2.0)	HClO4 (5)	60	CH_3CN	2	nd	nd	nd
6	5	$K_2S_2O_8$ (2.0)	TfOH (5)	60	CH_3CN	2	93 (76)	nd	7
7	5	$K_2S_2O_8$ (2.0)	TfOH (5)	80	CH_3CN	2	91 (74)	nd	9
8	5	$K_2S_2O_8$ (2.0)	TfOH (5)	RT	CH_3CN	12	90 (74)	nd	10
9	5	$K_2S_2O_8$ (2.0)	TfOH (5)	RT	none	12	72 (55)	(10)	13
10	5	$K_2S_2O_8$ (2.0)	TfOH (3)	60	CH_3CN	2	63	nd	37
11	5	$K_2S_2O_8$ (2.0)	TfOH (4)	60	CH_3CN	2	63	nd	37
12	3	$K_2S_2O_8$ (2.0)	TfOH (5)	60	CH_3CN	2	81 (63)	nd	19
13	4	$K_2S_2O_8$ (2.0)	TfOH (5)	60	CH_3CN	2	81 (70)	nd	19
14	**4**	**$K_2S_2O_8$ (3.0)**	**TfOH (5)**	**60**	**CH_3CN**	**2**	**(86)**	**nd**	**nd**
15	5	$(NH_4)_2S_2O_8$ (2.0)	TfOH (5)	80	CH_3CN	2	88 (73)	nd	12
16	5	oxone (2.0)	TfOH (5)	RT	CH_3CN	2	42	nd	58
17[c]	5	mCPBA (2.0)	TfOH (5)	RT	CH_3CN	2	trace	nd	nd
18	5	H_2O_2 (2.0)	TfOH (5)	60	CH_3CN	2	nd	nd	nd
19[c]	4	$K_2S_2O_8$ (3.0)	TfOH (5)	60	DMF	2	nd	nd	nd
20	4	$K_2S_2O_8$ (3.0)	TfOH (5)	60	DCE	6	83 (60)	7	10
21	5	none	TfOH (5)	RT	none	12	nd	(42)	nd

[a]Reaction conditions: **1a** (0.25 mmol). nd = not detected. In entries 1−3 and 5, starting material was observed (TLC). [b]^{1}H NMR conversion. Values in parentheses are isolated yields. [c]Starting material decomposed.

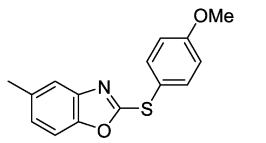
dx.doi.org/10.1021/jo501793q | J. Org. Chem. 2014, 79, 9655−9668

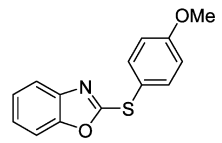
Table 2. Thiolation of Anisole and Its Derivatives[a]

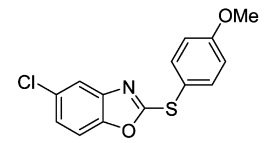


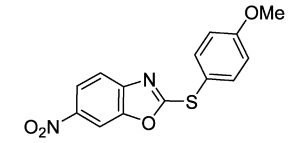
1a: R^1= Me, R^2= H, X=O
1b: R^1= R^2= H, X=O
1c: R^1= Cl, R^2= H, X=O
1d: R^1= H, R^2= NO_2, X=O
1e: R^1= H, R^2= Me, X=O
1f: naphtho[1,2-*d*]oxazole-2(1*H*)-thione
1g: R^1= R^2= H, X=S

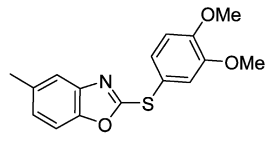
2a: anisole
2b: 1,2-dimethoxybenzene
2c: 1,3-dimethoxybenzene
2d: 1,2,3-trimethoxybenzene
2e: benzo[*d*][1,3]dioxole
2f: 1-methoxy-3,5-dimethylbenzene
2g:1-methoxy-2,3-dimethylbenzene
2h: thioanisole

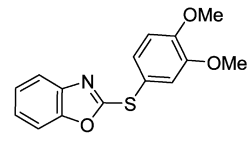

3a (86%)

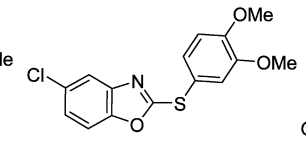

3b (54%)[b]

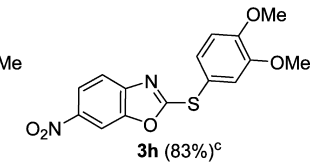

3c (63%)

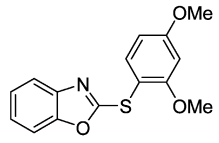

3d (48%)[c]

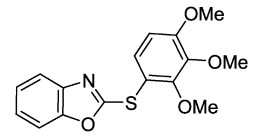

3e (89%)

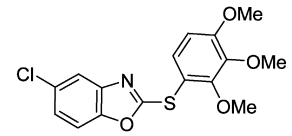

3f (87%)[b]

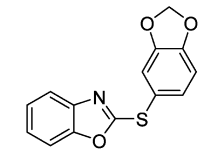

3g (82%)

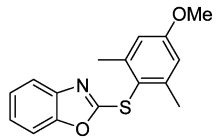

3h (83%)[c]

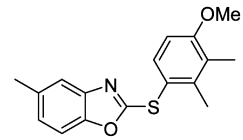

3i (95%)[b]

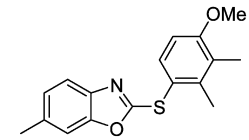

3j (85%)[d]

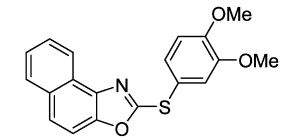

3k (90)[d]

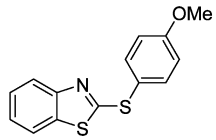

3l (37%)[b]

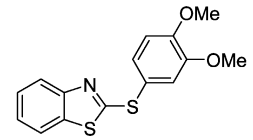

3m (90%)

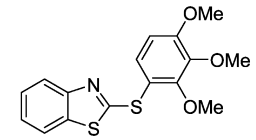

3n (95%

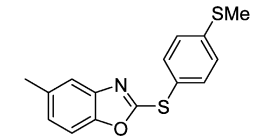

3o (95%)


3p (52%)


3q (0%)


3r (28%)[b]


3s (52%)[d]

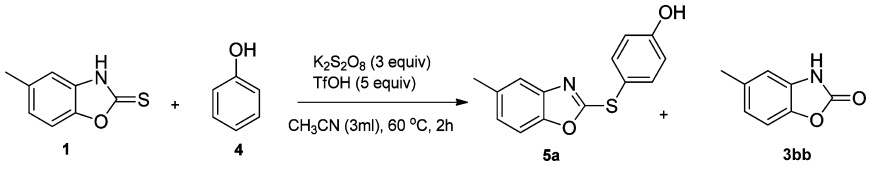

3t (79%)

[a]Reaction conditions unless otherwise noted: **1** (0.25 mmol), **2** (1 mmol). [b]Reaction conditions: **1** (0.5 mmol), **2** (2 mmol). [c]For 4 h. [d]A 2 equiv amount of 1,2,3-trimethoxybenzene was used.

or under solvent-free conditions required a longer reaction time (12 h) and furnished **3a** as a major product along with minor amounts of **3aa** and **3bb** (entries 8 and 9). Further studies (entries 10−14) indicated that 3 equiv of $K_2S_2O_8$, 5 equiv of TfOH, and 4 equiv of **2a** in CH_3CN at 60 °C for 2 h are optimal reaction conditions to obtain **3a** as the sole product in good yield (86%, entry 14, Table 1). Although $(NH_4)_2S_2O_8$ (2 equiv) was a useful oxidant, it furnished **3a** as a major product along with the oxidized product **3bb** (12%, entry 15, Table 1). Further screening studies to find a suitable oxidant revealed that the utility of oxone (2 equiv) resulted in the formation of **3a** and **3bb** in 42% and 58% yields, respectively (entry 16), whereas *m*-CPBA

dx.doi.org/10.1021/jo501793q | J. Org. Chem. 2014, 79, 9655−9668

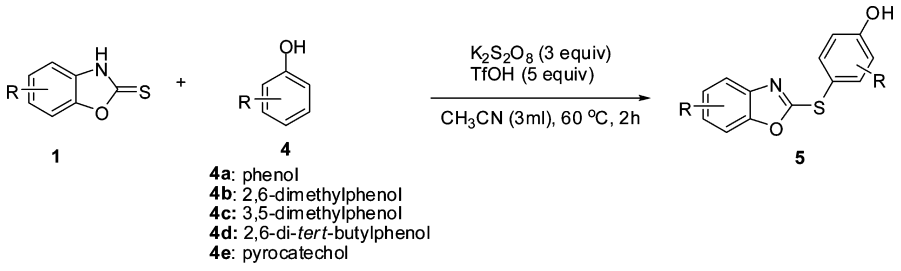
Table 3. Optimization of the Reaction Conditions for the Reaction of 1a with Phenol[a]



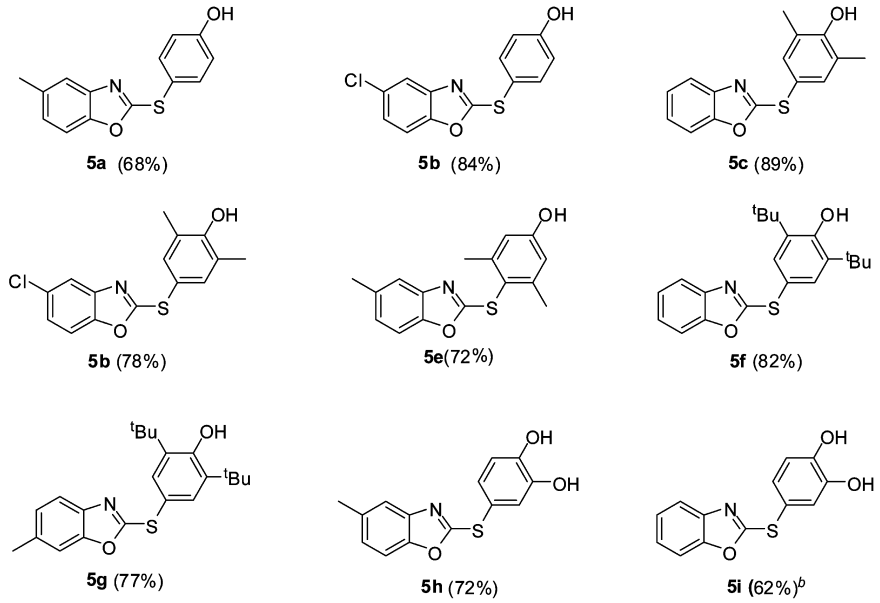
entry	3a (equiv)	oxidant (equiv)	yield (%) 5a	yield (%) 3bb
1	2	$K_2S_2O_8$ (2.0)	40	10%
2	2	$K_2S_2O_8$ (3.0)	54	10%
3	3	$K_2S_2O_8$ (3.0)	62	trace
4	**4**	**$K_2S_2O_8$ (3.0)**	**68**	**trace**

[a]Reaction conditions: **1a** (0.5 mmol), solvent (3 mL).

Table 4. CDC Reaction of Phenols with Benz[*d*]oxazole-2(3*H*)-thiones[a]



4a: phenol
4b: 2,6-dimethylphenol
4c: 3,5-dimethylphenol
4d: 2,6-di-*tert*-butylphenol
4e: pyrocatechol



[a]Reaction conditions unless otherwise noted: **1** (0.25 mmol), **4** (2 mmol). [b]Reaction conditions: **1b** (0.5 mmol), **4e** (2 mmol).

and H_2O_2 were not helpful in promoting the reaction (entries 17 and 18). In the solvent screening studies it was found that the starting material **1a** decomposed when DMF was used as the solvent, whereas a similar reaction in DCE formed a mixture of **3a**, **3aa**, and **3bb** in 83%, 7%, and 10% yields, respectively (entries 19 and 20). The reaction in the absence of oxidant under solvent-free conditions did not yield the expected product **3a** and furnished **3aa** in 42% isolated yield (entry 21, Table 1; see the Supporting Information for the mechanism, SI-Scheme 1).

To find the scope and limitation of the reaction, a variety of substituted thiones were treated with anisole derivatives (Table 2). Anisole (**2a**) underwent a facile reaction with thiones **1a**, **1b**, **1c**, and **1d** to furnish the thiolated products **3a**, **3b**, **3c**, and **3d** in good yields (86%, 54%, 63%, and 48%, respectively). Furthermore, **2b** reacted well with **1a**, **1b**, **1c**, and **1d** to afford the products **3e**, **3f**, **3g**, and **3h** in 89%, 87%, 82%, and 83% yields, respectively. Similarly, **2c** reacted with **1b** to furnish the coupled product **3i** in excellent yield (95%). 3,4,5-Trimethoxyphenyl thioether derivatives are a commonly found scaffold in anticancer compounds.[3l,13] In light of this information, 1,2,3-trimethoxybenzene (**2d**; 2 equiv) was subjected to a coupling reaction with thiones **1b**, **1c**, and **1d** to obtain the products **3j** and **3k** in good yields (85% and 90%, respectively). As trimethoxybenzene is a highly electron rich system, the reaction proceeded well with 2

dx.doi.org/10.1021/jo501793q | J. Org. Chem. 2014, 79, 9655−9668

equiv of trimethoxybenzene. Furthermore, **1b** reacted well with **2e** and **2f** to afford the products **3l** and **3m** (37% and 90% yields, respectively). Under the optimal reaction conditions, **2g** underwent a facile reaction with **1a** and **1e** to form **3n** and **3o** in 95% yield. Naphth[2,3-*d*]oxazole-2(3*H*)-thione (**1f**) was coupled with **2b** to form the corresponding thionated product **3p** in 52% yield. Under the optimal reaction conditions, thione **1g** was found to be less reactive. Reaction of **1g** with **2a** and 1,2-dimethoxybenzene (**2b**) as well as **2d** furnished the products **3q**, **3r**, and **3s** (0%, 28%, and 52% yields, respectively). Interestingly, thioanisole (**2h**) also underwent a facile reaction with **1a** to afford the product **3t** in 79% yield.

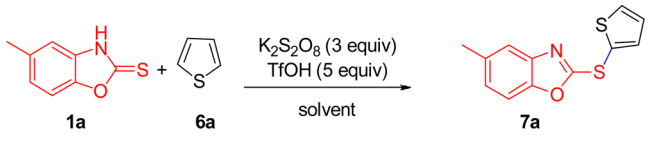
The reactions of anisole derivatives with a variety of thiones prompted us to examine the reactions of phenol derivatives under similar reaction conditions (Table 3). As can be seen from the quick screening studies, the reaction conditions required are almost similar to those adopted for anisole. It was observed that decreasing the amount of phenol or $K_2S_2O_8$ led to the formation of 5-methylbenzoxazol-2-one as a byproduct (entries 1 and 2, Table 3). It was found that the reactions furnishes **5a** in major amounts by using 3−4 equiv of phenol and 3 equiv of $K_2S_2O_8$ (62% and 68% yields, respectively, entries 3 and 4, Table 3). Hence, the optimal reaction conditions for reaction of **1a** with phenol (**4a**) to obtain **5a** in good yield (68%, entry 4, Table 3) are 4 equiv of **4a**, 3 equiv of $K_2S_2O_8$, and 5 equiv of TfOH in CH_3CN at 60 °C for 2 h.

Under the optimized reaction conditions, phenol (**4a**) underwent a CDC reaction with thiones **1a** and **1c** to afford **5a** and **5b** in moderate to excellent yields (68% and 84%, respectively, Table 4), whereas 2,6-dimethylphenol (**4b**) reacted well with thiones **1b** and **1c** to form **5c** and **5d** in good yields (89% and 78%, respectively). 3,5-Dimethylphenol (**4c**) was found to react well with **1a** to afford **5e** in 72% yield. Similarly, the coupling reaction of 2,6-di-*tert*-butylphenol (**4d**) with thiones **1b** and **1e** resulted in the formation of the products **5f** and **5g** in good yields (82% and 77%, respectively). To expand the scope of this CDC reaction, catechol (**4e**) was reacted with **1a** and **1b** to obtain the products **5i** and **5j** in good yields (72% and 62%, respectively).

The regioselective CDC reaction of thione derivatives with anisole and phenol to form C−S bonds has encouraged us to explore further possibilities. It is known that thiophene-containing thioethers are potential lipoxygenase inhibitors,[14] and it is also well-known that thiophene is a relatively less reactive aromatic heterocycle. In this direction, preliminary screening studies of **1a** with thiophene (**6a**) revealed that the reaction is facile and proceeds well at room temperature. As can be seen in Table 5, either increasing the temperature or extending the reaction time was not helpful in furnishing **7a** in good yields (entries 1−4, Table 5). Finally, a good yield of **7a** was furnished by performing the reaction of thiophene (10 equiv) with **1a** using $K_2S_2O_8$ (3 equiv) and TfOH (5 equiv) in CH_3CN at rt (entry 5, 75%, Table 5). However, the reactions under solvent-free conditions or in DCE were not helpful (entries 6 and 7, Table 5).

Under the optimized conditions, the reaction of **1a** and **1b** with excess thiophene (**6a**) in the presence of $K_2S_2O_8$ (3 equiv) and TfOH (5 equiv) in CH_3CN at rt furnished the compounds **7a** and **7b** (75% and 52% yields, respectively, Table 6). Similarly, 2-methylthiophene (**6b**) and 2,5-dimethylthiophene (**6c**) at 60 °C underwent thiolation with **1b** and **1a** to furnish the products **7c**, **7d**, and **7e** (72%, 80%, and 74%, respectively, Table 6). The coupling reaction of benzo[*b*]thiophene (**6d**; 4 equiv) with **1a** and **1b** at room temperature proceeded well to furnish **7f** and **7g** in 72% and 73% yields, respectively. Similarly, **1f** underwent a similar coupling reaction with **6d** under the optimal reaction conditions to form the product **7h** in low yield (23%). As can be seen in the molecular structure diagrams (Table 6, see Supporting Information for ORTEP diagram of **7a** and 7g), the thiolation of thiophene derivatives has taken place at the C-2 position (**7a**−**7d**). However, a similar reaction of benzothiophene led to C−S bond formation at C-3 (**7f**−**7h**).

Table 5. Optimization of the Reaction Conditions for Reaction of 1a with Thiophene[a]



1a **6a** **7a**

entry	**6a** (equiv)	solvent (°C)	time (h)	yield (%)
1	4	CH_3CN (RT)	24	36
2	4	CH_3CN (60°C)	6	29
3	8	CH_3CN (60°C)	2	56
4	10	CH_3CN (60°C)	2	60
5	**10**	**CH_3CN (RT)**	**12**	**75**
6	10	Neat (RT)	12	trace
7	10	DCE (RT)	12	trace

[a]Reaction conditions: **1a** (0.5 mmol), solvent (3 mL).

The regioselective reaction of thione with anisole, phenol, and thiophene led us to perform the reaction of thiones with 1,4-dimethoxybenzene or 1,3,5-trimethoxybenzene. Hence, **1a** was reacted with 1,4-dimethoxybenzene (**8a**) at 60 °C for 10 h to obtain the corresponding thionated product 2-((2,5-dimethoxyphenyl)thio)-5-methylbenz[*d*]oxazole (**9**) in 38% yield (Scheme 2). The thiolation of 1,3,5-trimethoxybenzene (**8b**; 2 equiv) with **1a** and **1d** afforded the monosubstituted products 2-((2,4,6-trimethoxyphenyl)thio)-5-methylbenz[*d*]-oxazole (**10a**) and 6-nitro-2-((2,4,6-trimethoxyphenyl)thio)-benz[*d*]oxazole (**10b**) in good yields (80% and 81%, respectively).

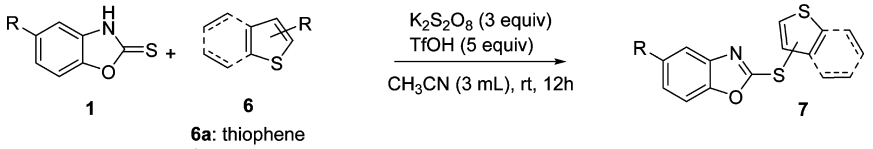
It was interesting to observe that a similar reaction of benzothiazole-2-thione (**1g**; 0.5 equiv) with **8b** (1 equiv) under reaction conditions similar to those adopted for 5-methylbenz-[*d*]oxazole-2(3*H*)-thione (**1a**) resulted in the formation of a mixture of mono- and dithionated products **11a** and **11b** in 66% yield in a 1:1 ratio. Further efforts to obtain di- and trithionated products using excess **1g** (2 or 4 equiv) resulted in the formation of dithionated product **11b** in 25% and 27% yields, respectively (Scheme 3).

Our attempts to react alkyl-substituted aromatic systems such as toluene or xylene under the optimal reaction conditions were not successful. However, the reaction of 5-methylbenzoxazole-2-thione (**1a**) with excess mesitylene at 60 °C resulted in the formation of the corresponding thiolated product **13** in 71% yield (Scheme 4).

To find the selectivity in the reaction of 5-methylbenzoxazole-2-thione (**1a**) with anisole (**2a**), phenol (**4a**), thioanisole (**2h**), and 2-methoxyphenol (**14**) under the optimal reaction conditions, the reactions in Scheme 5 were performed. As can be seen in the reaction of **1a** with anisole and thioanisole, anisole was found to react preferentially over thioanisole. Similarly, phenol was found to react preferentially over anisole. These experiments suggest that the reaction is highly regio- and chemoselective and the order of chemoselectivity is as follows: phenol > anisole > thioanisole. The structure of **15** was confirmed by X-ray crystallography.

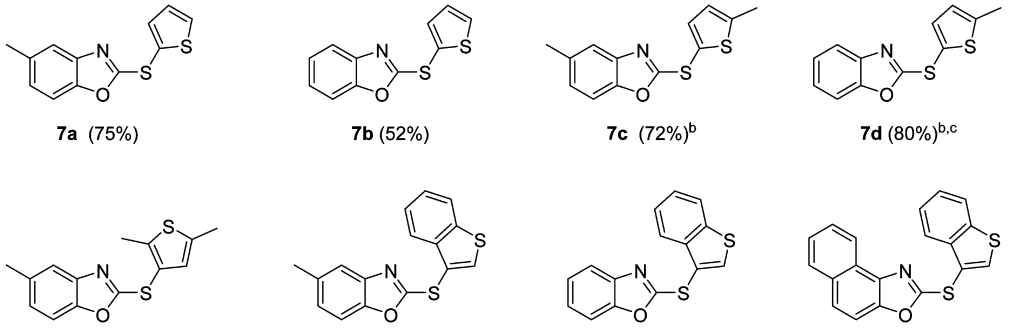
dx.doi.org/10.1021/jo501793q | *J. Org. Chem.* 2014, 79, 9655−9668

Table 6. CDC Reaction of Thiophene with Benz[*d*]oxazole-2(3*H*)-thiones[a]



1 6 7

6a: thiophene
6b: 2-methylthiophene
6c: 2,5-dimethylthiophene
6d: benzothiophene

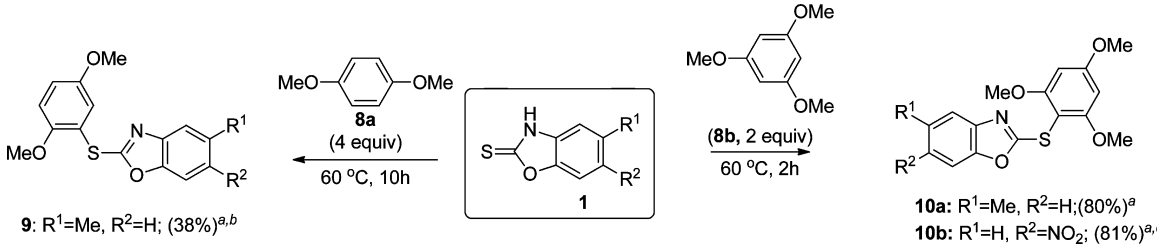


7a (75%) **7b** (52%) **7c** (72%)[b] **7d** (80%)[b,c]

7e (74%)[b] **7f** (72%)[d,e] **7g** (61%)[d] **7h** (23%)[d,e]

[a]Reaction conditions unless otherwise noted: **1** (0.5 mmol), **6** (5 mmol). [b]At 60 °C for 2 h. [c]Reaction conditions: **1b** (0.25 mmol), **6b** (2.5 mmol). [d]At rt for 12 h using **6d** (2 mmol). [e]Reaction conditions: **1** (0.25 mmol), **6d** (1 mmol).

Scheme 2. Reaction of Thione with Trimethoxybenzene and Dimethoxybenzene

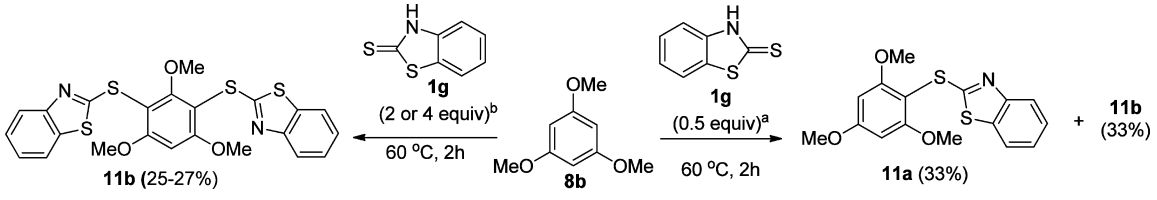


9: R^1=Me, R^2=H; (38%)[a,b] **1**

10a: R^1=Me, R^2=H;(80%)[a]
10b: R^1=H, R^2=NO_2; (81%)[a,c]

[a]Reaction conditions unless otherwise noted: **1** (0.25 mmol), $K_2S_2O_8$ (3 equiv), CH_3CN (3 mL). Isolated yields in parentheses. [b]**1a** (0.5 mmol) was used. [c]For 4 h.

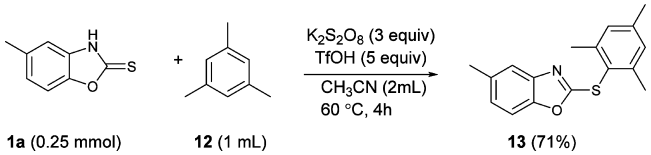
Scheme 3. Thiolation of 1,3,5-Trimethoxybenzene (8b) with Benzothiazole-2-thione (1g)



11b (25-27%) **11a** (33%)

[a]Reaction conditions: **8b** (1 mmol), **1g** (0.5 mmol), $K_2S_2O_8$ (3 equiv), TfOH (5 equiv), CH_3CN (3 mL). [b]Reaction conditions: **8b** (0.25 mmol), **1g** (0.5 or 1 mmol), $K_2S_2O_8$ (3 equiv), TfOH (5 equiv), CH_3CN (3 mL).

Scheme 4. Thiolation of Mesitylene (12) with 5-Methylbenzoxazole-2-thione (1a)

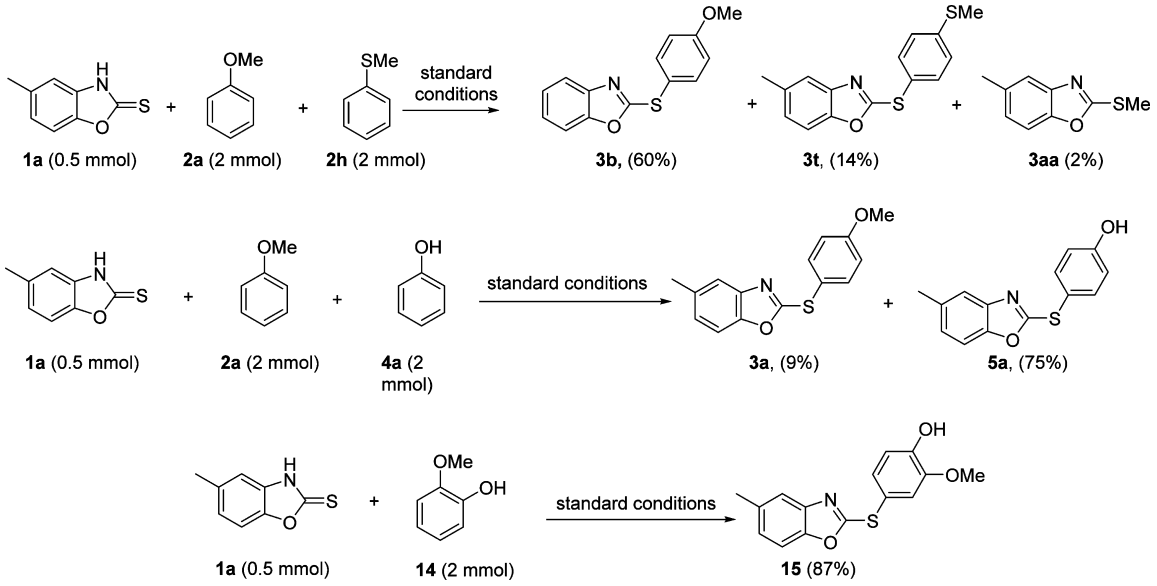


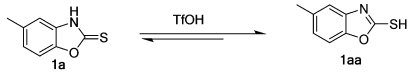
1a (0.25 mmol) **12** (1 mL) **13** (71%)

Mechanistic Considerations. To follow the reaction pathway of the thiolation reaction, the following experiments were performed. On the basis of the screening studies (Table 1), the tautomerization of benz[*d*]oxazole-2-thione is critical for the thiolation to proceed. On the basis of the literature precedence and to ensure the equilibrium of benz[*d*]oxazole-2-thione in acidic media, the ^{1}H NMR sepctrum of 5-methylbenz[*d*]oxazole-2-thione (**1a**) in either TFA or TfOH in CD_3CN was recorded. It is clearly observed that the ^{1}H NMR spectrum of **1a** in thione form (Figure 2, entry 1) shows a singlet for the CH_3 group at δ 2.39 (Figure 3, spectrum i) and that of the thiol form of **1a** (Figure 2, **1aa**) appears at δ 2.56 (Figure 3, spectrum iv). As can be seen from Figures 2 and 3, the thione **1a** exclusively exists in

dx.doi.org/10.1021/jo501793q | J. Org. Chem. 2014, 79, 9655−9668

Scheme 5. Chemoselective Reactions of Phenol, Anisole, Thioanisole, and 2-Methoxyphenol with 1a





entry	Brønsted acid (equiv)	1a:1aa
1	none	1:0
2	TFA (5))	1:0
3	TfOH (3)	1: 0.31
4	**TfOH (5)**	**0:1**

Figure 2. Tautomerism of **1a**.

thiol form in 5 equiv of TfOH (Figure 2, entry 4), whereas in TFA or in a lower amount of TfOH (3 equiv) the equilibrium shifts toward the thione form (Figure 2, entries 2 and 3, respectively). This observation is in good agreement with the optimization study, which indicates that the reaction does not proceed with other acids (entries 1−5, Table 1) and the reaction furnishes a lower yield with fewer equivalents of TfOH (entries 10 and 11). These preliminary NMR studies indicate that the thiol form exists exclusively when 5 equiv of TfOH is used.

Further investigation in this direction revealed that the protonation of nitrogen in benzothiazole or benzoxazole is important and needs a very strong acid. The reaction of disulfide **16** with 1,3,5-trimethoxybenzene (**8b**) in TfOH (10 equiv) *in the absence of oxidizing agent* $K_2S_2O_8$ furnished the corresponding thiolated product **11a** and benzothiazole-2-thione (**1g**) along with monosulfide **17** in a considerable amount (27%, Scheme 6; also see the Supporting Information, SI-Scheme 2).

Additionally, the reaction of 5-methylbenzoxazole-2-thione (**1a**) with anisole (**2a**) under standard conditions in the presence of radical inhibitor BHT (3 equiv) did not furnish the product **3a**, indicating that the reaction proceeds through the corresponding thioradical. Similarly, the reaction of **1a** with **2a** under optimal conditions in the presence of TEMPO resulted in a decrease of the yield of the expected product **3a** to 60%.[15] A tentative mechanism has been proposed on the basis of the above studies (Scheme 7). The benzazole-2-thio radical that has been generated by the reaction of benzazole with $K_2S_2O_8$ forms either the corresponding disulfide or a benzazole persulfate adduct in which the nitrogen is protonated (intermediates **1** and **2**, Scheme 7). These intermediates further react with the electron-rich aromatic system to furnish the products. However, a similar reaction of thiophenol with anisole under the optimal reaction conditions did not yield the expected thiolated product. Further studies are under way to substantiate this observation.

CONCLUSION

In conclusion, we have described an unprecedented CDC reaction for the formation of a C−S bond by utilizing thione as a masked thiol. The method, although limited to electron-rich partners, nonetheless provides an elegant and new avenue for synthesizing thioethers, despite the propensity of thiols to easily undergo oxidation. This strategy provides a rare opportunity to use thione in the CDC reaction to form C−S bonds to obtain arylthiobenzoxazoles, heteroarylthiobenzoxazoles, and arylthiobenzothiazoles, which are pharmaceitically valuable compounds. This highly regioselective CDC reaction is unique as it requires the reversal of the reactivity of sulfur to form the C−S bonds.

EXPERIMENTAL SECTION

General Procedures. All reactions were carried out using distilled solvents. Reactions were monitored by using precoated silica TLC plates. Mass spectra were recorded in EI and ESI (TOF) modes. NMR spectra were recorded at 400 MHz. Column chromatography was carried out with 100−200 mesh silica gel. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

Typical Procedure for the Preparation of Benz[*d*]oxazole-2(3*H*)-thione Derivatives Using 5-Methylbenz[*d*]oxazole-2(3*H*)-thione (1a) as an Example.[16] To a well-stirred, ice-cold solution of 2-amino-4-methylphenol (6.15 g, 0.05 mol) and KOH or K_2CO_3 (0.075 mmol) in an ethanol−water mixture (1:0.5, 30 mL) was added CS_2 (0.075 mol, 5.7 g, 4.5 mL) dropwise. After complete addition of CS_2, the reaction mixture was allowed to attain room temperature followed by heating at 80 °C for 8 h. The reaction mixture was then cooled to room temperature, water was added (50 mL), the mixture was acidified with 2 N HCl, and the solid precipitated was filtered. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 30:70) to give **1a** (90%, 7.4 g).

Typical Procedure for the Preparation of Naphth[1,2-*d*]oxazole-2(1*H*)-thione (1f). To a well-stirred, ice-cold solution of 1-amino-2-naphthol hydrochloride salt (1 g, 5.1 mmol), K_2CO_3 (1.05 g, 5.6 mmol), and triethylamine (772 mg, 5.6 mmol) in an ethanol−water mixture (1:0.5, 30 mL) was added CS_2 (581 mg, 7.66 mmol, 0.46 mL) dropwise. After complete addition of CS_2, the reaction mixture was

dx.doi.org/10.1021/jo501793q | J. Org. Chem. 2014, 79, 9655−9668

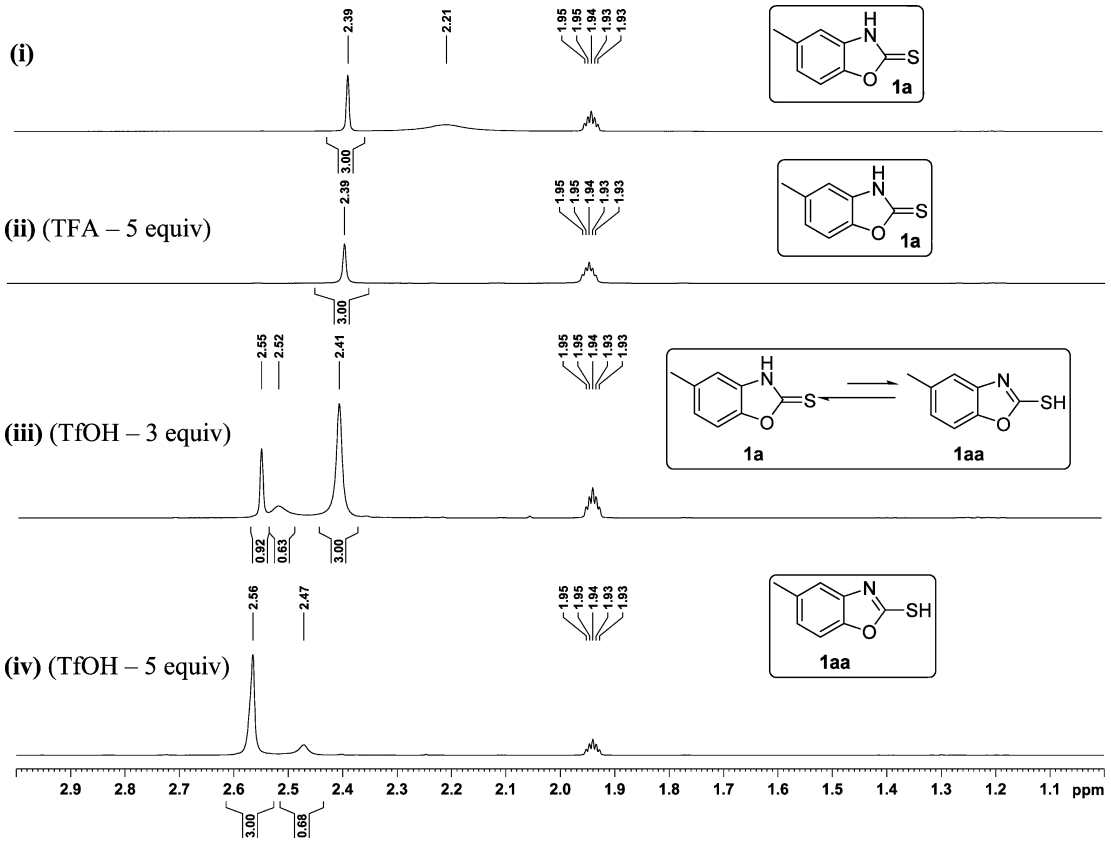
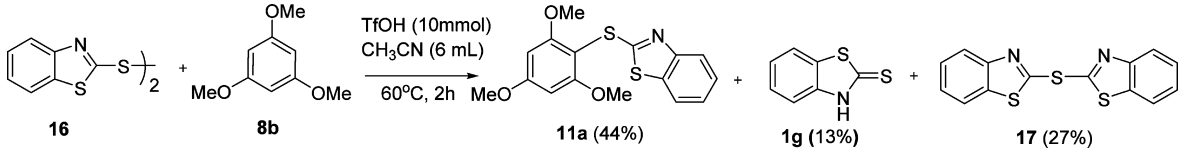


Figure 3. ^{1}H NMR experiments: (i) **1a** (4.5 mg) in CD_3CN (0.5 mL); (ii) **1a** (1 equiv) in TFA (5 equiv) and CD_3CN (0.45 mL); (iii) **1a** (41.25 mg) in TfOH (3 equiv) and CD_3CN (0.94 mL); (iv) **1a** (20.5 mg) in TfOH (5 equiv) and CD_3CN (0.45 mL).

Scheme 6. Reaction of Disulfide with Trimethoxybenzene[a]



[a]Reaction conditions: **15** (1.0 mmol), **8b** (4.0 mmol).

allowed to attain room temperature followed by heating at 80 °C for 8 h. The reaction mixture was then cooled to room temperature, water awas dded (50 mL), the mixture was acidified with 2 N HCl, and the solid precipitated was filtered. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 30:70) to give **1f** (70%, 1.4 g).

Typical Procedure for the Reaction of Anisole or Phenol with 5-Methylbenz[*d*]oxazole-2(3*H*)-thione To Give 3a−3t and 5a−5i Using 3a as an Example. To a well-stirred, ice-cold solution of **1a** (41.25 mg, 0.25 mmol), anisole[17] (108 mg, 1 mmol), and $K_2S_2O_8$ (202.5 mg, 0.75 mmol) in CH_3CN (3 mL) was added TfOH (187.6 mg, 1.25 mmol, 0.11 mL) dropwise over 3 min. The reaction mixture was allowed to attain room temperature followed by heating at 60 °C for 2 h. The reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was cooled to room temperature, water was added (50 mL), and the crude compound was extracted with DCM (20 mL × 3), dried over Na_2SO_4, and purified on a silica gel column (EtOAc/petroleum ether, 5:95) to obtain **3a** (59 mg, 86%).

Typical Procedure for the Reaction of Thiophene with 5-Methylbenz[*d*]oxazole-2(3*H*)-thione To Give 7a−7h Using 7a as an Example. To a well-stirred, ice-cold solution of **1a** (82.5 mg, 0.5 mmol), thiophene[18] (**6a**; 420 mg, 5 mmol), and $K_2S_2O_8$ (405 mg, 1.5 mmol) in CH_3CN (3 mL) was added TfOH (375 mg, 2.5 mmol) dropwise. The reaction mixture was allowed to attain room temperature, and stirring was continued for 12 h. The reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was cooled to room temperature, water was added (50 mL), and the crude compound was extracted with DCM (20 mL × 3), dried over Na_2SO_4, and purified on a silica gel column (EtOAc/petroleum ether, 3:97) to obtain **7a** (92 mg, 75%).

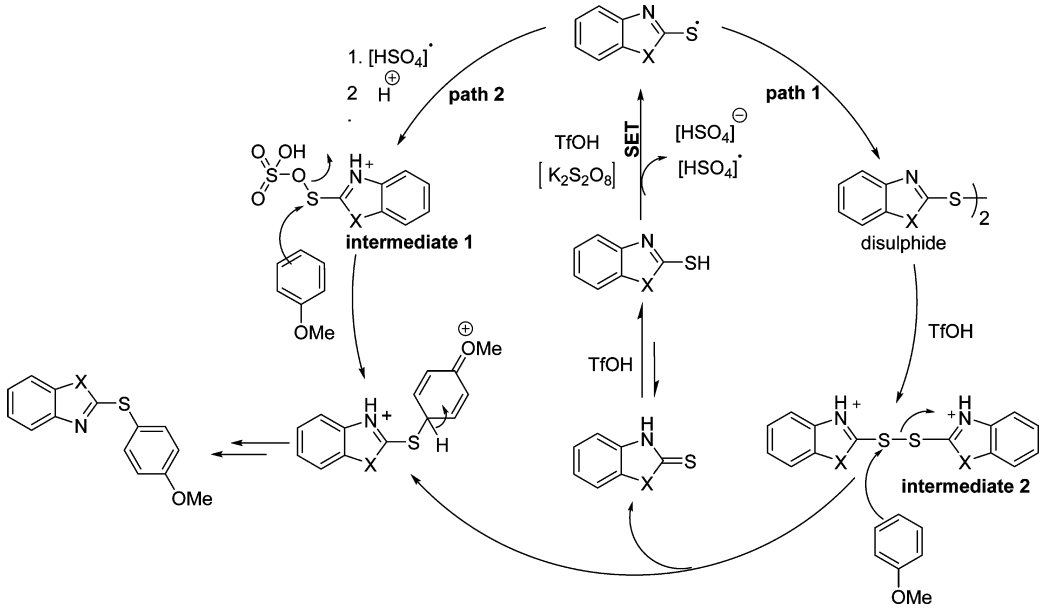
Note: For 2-methylthiophene (**6b**) and 2,5-dimethylthiophene (**6c**) the reactions were carried out at 60 °C for 2 h.

Synthesis of Reference Compound 5-Methylbenz[*d*]oxazol-2(3*H*)-one (3bb).[19] To a stirred ice-cold solution of 2-amino-4-methylphenol (10 mmol, 1.23 g) in dioxane (20 mL) was added ethyl chloroformate (10 mmol, 1.08 g) dropwise over 4−5 min. After complete addition of ethyl chloroformate, the reaction mixture was allowed to attain room temperature and stirred 4 h. The reaction was monitored by TLC. After complete conversion of starting material, the solvent was evaporated, and 20 mL of ethanol and 10 mL of 2 N HCl were added to the crude compound followed by reflux at 80 °C for 4 h. The solvent was evaporated. A 20 mL volume of water was added to the crude compound, and the crude compound was extracted with EtOAc (20 mL × 3), dried over Na_2SO_4, and purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 30:70) to give **3bb** in 60% yield (0.894 g).

^{1}H NMR Experimental Procedure. (i) The ^{1}H NMR spectrum of **1a** (4.5 mg) in CD_3CN (0.5 mL) was recorded. (ii) To a mixture of **1a**

dx.doi.org/10.1021/jo501793q | J. Org. Chem. 2014, 79, 9655−9668

Scheme 7. Proposed Mechanism



(21 mg, 0.125 mmol, 1 equiv) in CD_3CN (0.45 mL) was added TFA (0.05 mL, 0.625 mmol, 5 equiv), and 0.1 mL of this heterogeneous solution was diluted to 0.5 mL using CD_3CN. The ^1H NMR spectrum was recorded. (iii) To a mixture of **1a** (41.25 mg, 0.250 mmol, 1 equiv) in CD_3CN (0.94 mL) was added TfOH (0.066 mL, 0.748 mmol, 3 equiv), and the solution turned homogeneous. The ^1H NMR spectrum was recorded. (iv) To a mixture of **1a** (20.5 mg, 0.125 mmol, 1 equiv) in CD_3CN (0.45 mL) was added TfOH (0.05 mL, 0.625 mmol, 5 equiv), and the solution turned homogeneous. The ^1H NMR spectrum was recorded.

^1H NMR data for **1a** in CD_3CN (400 MHz, CD_3CN): δ (ppm) 10.96 (br s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.07−7.05 (m, 2H), 2.38 (s, 3H).

^1H NMR data for **1a** (21 mg, 1 equiv) and TFA (71.25 mg (0.05 mL), 5 equiv) in CD_3CN (0.45 mL) (400 MHz, CD_3CN): δ (ppm) 10.96 (br s, 1H), 7.24 (d, J = 8.6 Hz, 1H), 7.07−7.05 (m, 2H), 2.39 (s, 3H).

Characterization Data: Precursors 1a−1f. *5-Methylbenz[d]-oxazole-2(3H)-thione (**1a**).*[20] **1a** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 30:70). White solid. Yield: 90% (7.4 g). Mp: 224−226 °C (lit.[20] 220−223 °C). R_f (10% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 2924, 2854, 1622, 1460, 1468. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.76 (br s, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.06−7.04 (m, 2H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 180.2, 146.3, 134.8, 131.2, 124.3, 110.5, 109.5, 20.8. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for C_8H_7NNaOS 188.0146, found 188.0147.

*Benz[d]oxazole-2(3H)-thione (**1b**).*[21] **1b** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 30:70). White solid. Yield: 90% (6.75 g). Mp: 195−197 °C (lit.[21] 191 °C). R_f (10% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1616, 1507, 1447, 1420, 1131. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.9 (br s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.31−7.23 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 180.1, 148.1, 131.2, 125.2, 123.8, 110.5, 110.1. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for C_7H_5NNaOS 173.9990, found 173.9994.

*5-Chlorobenz[d]oxazole-2(3H)-thione (**1c**).*[20] **1c** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). White solid. Yield: 85% (7.82 g). Mp: 270−272 °C (lit.[22] 268 °C). R_f (10% EtOAc/hexane): 0.2. IR (KBr, cm^{-1}): 3098, 3061, 1607, 1513, 1455, 1462, 1422, 1264. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 14.01 (br s, 1H), 7.51 (d, J = 8.9 Hz, 1H), 7.06−7.04(m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 180.7, 146.9, 132.5, 129.3, 123.5, 111.2, 110.3. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_7H_4ClONNaS$ 207.9600, found 207.9600.

*6-Nitrobenz[d]oxazole-2(3H)-thione (**1d**).* **1d** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). White solid. Yield: 85% (8.33 mg). mp 235−237 °C (lit.[23] 234−235 °C). R_f (20% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 3045, 2929, 1613, 1536, 1518, 1478, 1410, 1377, 1347. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 14.45−14.37 (br, m, 1H), 8.39 (d, J = 1.5 Hz, 1H), 8.20 (dd, J_1 = 8.7 Hz, J_2 = 1.6 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 181.9, 147.5, 143.4, 137.2, 121.7, 110.1, 106.0. MS (m/z): 196 (M^+).

*6-Methylbenz[d]oxazole-2(3H)-thione (**1e**).*[24] **1e** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 30:70). White solid. Yield: 90% (7.4 g). Mp: 212−213 °C. R_f (10% EtOAc/hexane): 0.3. IR (KBr, cm^{-1}): 1628, 1500, 1425, 1218, 1156, 1099. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 13.76 (br s, 1H), 7.31 (s, 1H), 7.09 (s, 2H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 179.7, 148.3, 133.7, 128.8, 125.7, 110.2, 109.9, 20.8. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for C_8H_7NNaOS 188.0146, found 188.0142.

*Naphth[1,2-d]oxazole-2(1H)-thione (**1f**).* **1f** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). White solid. Yield: 70% (1.4 g). Mp: 238−241 °C (lit.[25] 248 °C). R_f (10% EtOAc/hexane): 0.5. IR (KBr, cm^{-1}): 2923, 2854, 1508, 1490, 1458. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 14.60 (br s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 8.9 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.67 (t, J = 7.3 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 179.5, 145.2, 130.5, 128.8, 127.4, 126.1, 125.8, 124.5, 121.2, 118.8, 110.4. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{11}H_7NNaOS$ 224.0146, found 224.0148.

Characterization Data: Products. *2-((4-Methoxyphenyl)thio)-5-methylbenz[d]oxazole (**3a**).* **3a** was prepared as described in the typical experimental procedure. Colorless liquid. Yield: 86% (58 mg). R_f (5% EtOAc/hexane): 0.25. IR (neat, cm^{-1}): 1593, 1492, 1480, 1251, 1146, 842. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (d, J = 8.7 Hz, 2H), 7.36 (s, 1H), 7.25 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 164.1, 161.1, 150.1, 142.2, 136.6, 134.0, 125.0, 118.9, 117.2, 115.2, 109.2, 55.3, 21.4. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{15}H_{14}NO_2S$ 272.0745, found 272.0745.

dx.doi.org/10.1021/jo501793q | J. Org. Chem. 2014, 79, 9655−9668

*2-((4-Methoxyphenyl)thio)benz[d]oxazole (**3b**).*[5d] **3b** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). Colorless solid. Yield: 54% (69 mg). Mp: 48−50 °C. R_f (10% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1590, 1494, 1453, 1249. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63 (2H, d, J = 8.9 Hz), 7.57 (1H, d, J = 6.3 Hz), 7.40−7.38 (1H, m), 7.26−7.21 (2H, m), 6.97 (2H, d, J = 8.8 Hz), 3.84 (3H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 164.4, 161.2, 151.8, 142.0, 136.7, 124.2, 124.0, 118.9, 116.9, 115.3, 109.9, 55.4. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{14}H_{12}NO_2S$ 258.0559, found 258.0585.

*5-Chloro-2-((4-methoxyphenyl)thio)benz[d]oxazole (**3c**).* **3c** was prepared as described in the typical experimental procedure. Colorless liquid. Yield: 63% (46 mg). R_f (20% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1679, 1521, 1250, 1129,1019. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 1.7 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.18 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 166.2, 161.3, 150.4, 143.1, 136.8, 129.7, 124.1, 118.8, 116.4, 115.3, 110.5, 55.4. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{14}H_{10}ClNNaO_2S$ 314.0018, found 314.0020.

*2-((4-Methoxyphenyl)thio)-6-nitrobenz[d]oxazole (**3d**).* **3d** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 10:90). Brown solid. Yield: 48% (36 mg). Mp: 120−122 °C. R_f (10% EtOAc/hexane): 0.2. IR (KBr, cm^{-1}): 1597, 1494, 1338, 1299, 1255, 1133. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.31 (d, J = 2.0 Hz, 1H), 8.23 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 7.65−7.61 (m, 3H), 7.02 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 170.7, 161.6, 150.9, 147.3, 144.1, 137.0, 120.7, 118.4, 115.5, 115.4, 106.3, 55.4. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{14}H_{11}N_2O_4S$ 303.0440, found 303.0444.

*2-((3,4-Dimethoxyphenyl)thio)-5-methylbenz[d]oxazole (**3e**).* **3e** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 5:95 to 10:90). White solid. Yield: 89% (67 mg). Mp: 111.5−112.5 °C. R_f (10% EtOAc/hexane): 0.25. IR (KBr, cm^{-1}): 1583, 1508, 1497, 1480, 1466, 1263, 1231. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 (s, 1H), 7.28−2.26 (m, 2H), 7.18 (1H, s), 7.03 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 2.4 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 163.9, 150.7, 150.1, 149.4, 142.2, 134.1, 128.3, 125.1, 119.0, 117.6, 117.3, 111.7, 109.3, 56.0, 55.9, 21.4. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{16}H_{15}NNaO_3S$ 324.0670, found 324.0695.

*2-((3,4-Dimethoxyphenyl)thio)benz[d]oxazole (**3f**).* **3f** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 5:95 to 10:90). White solid. Yield: 87% (125 mg). Mp: 86−88 °C. R_f (10% EtOAc/hexane): 0.3. IR (KBr, cm^{-1}): 1583, 1497, 1262, 1229, 1129. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 (d, J = 7.0 Hz, 1H), 7.42−7.40 (m, 1H), 7.31 (dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz, 1H), 7.28−7.22 (m, 2H), 7.19 (d, J = 1.4 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 164.2, 151.8, 150.8, 149.4, 142.0, 128.4, 124.3, 124.1, 118.9, 117.7, 117.1, 111.7, 109.9, 56.0, 55.9. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{15}H_{13}NNaO_3S$ 310.0514, found 310.0512.

*5-Chloro-2-((3,4-dimethoxyphenyl)thio)benz[d]oxazole (**3g**).* **3g** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 5:95 to 10:90). White solid. Yield: 82%. Mp: 112−114 °C. R_f (10% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1588, 1509, 1496, 1252, 1261, 1239. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 (d, J = 1.8 Hz, 1H), 7.32−7.28 (m, 2H), 7.21−7.17 (m, 2H), 6.94 (d, J = 8.5 Hz, 1H), 3.94 (s, 3H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 166.1, 151.0, 150.4, 149.5, 143.1, 129.8, 128.5, 124.2, 118.9, 117.7, 116.5, 111.8, 110.5, 56.1, 55.9. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{15}H_{12}ClNNaO_3S$ 344.0124, found 344.0126.

*2-((3,4-Dimethoxyphenyl)thio)-6-nitrobenz[d]oxazole (**3h**).* **3h** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 10:90 to 15:85). White solid. Yield: 83% (69 mg). Mp: 136−138 °C. R_f (20% EtOAc/hexane): 0.5. IR (KBr, cm^{-1}): 1506, 1347, 1262, 1233, 1135. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.31 (d, J = 1.8 Hz, 1H), 8.23 (dd, J_1 = 6.8 Hz, J_2 = 1.9 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.32 (dd, J_1 = 6.4 Hz, J_2 = 1.8 Hz, 1H), 7.18 (d, J = 1.8 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 170.6, 151.3, 150.9, 149.6, 147.3, 144.1, 128.8, 120.7, 118.4, 117.8, 115.4, 111.8, 106.4, 56.1, 56.0. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{15}H_{12}N_2NaO_5S$ 355.0365, found 355.0367.

*2-((2,4-Dimethoxyphenyl)thio)benz[d]oxazole (**3i**).* **3i** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 5:95 to 10:90). Faint yellow solid. Yield: 95% (137 mg). Mp: 88−90 °C. R_f (10% EtOAc/hexane): 0.3. IR (KBr, cm^{-1}): 1600, 1470, 1452, 1306, 1286, 1209. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60−7.56 (m, 2H), 7.37 (d, J = 7.7 Hz, 1H), 7.25−7.17 (m, 2H), 6.58−6.56 (m, 2H), 3.85 (s, 3H), 3.80 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 164.2, 163.3, 160.9, 151.8, 142.2, 137.8, 124.1, 123.7, 118.8, 109.8, 105.64, 105.60, 99.6, 56.0, 55.5. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{15}H_{13}NNaO_3S$ 310.0514, found 310.0517.

*2-((2,3,4-Trimethoxyphenyl)thio)benz[d]oxazole (**3j**).* **3j** was prepared as described in the typical experimental procedure. Yellow liquid. Yield: 85% (79 mg). R_f (10% EtOAc/hexane): 0.3. IR (KBr, cm^{-1}): 1557, 1408, 1295, 1237, 1223. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (d, J = 7.3 Hz, 1H), 7.42−7.39 (m, 2H), 7.26−7.20 (m, 2H), 6.75 (d, J = 8.7 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 164.0, 156.2, 154.7, 151.8, 143.0, 142.1, 131.0, 124.2, 123.9, 118.8, 112.0, 109.9, 107.8, 61.3, 60.1, 56.4. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{16}H_{15}NNaO_4S$ 340.0619, found 340.0620.

*5-Chloro-2-((2,3,4-trimethoxyphenyl)thio)benz[d]oxazole (**3k**).* **3k** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 10:90). White solid. Yield: 90% (85 mg). Mp: 68.5−69.5 °C. R_f (10% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1578, 1482, 1451, 1297, 1143, 1039. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (d, J = 1.8 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.18 (dd, J_1 = 8.7 Hz, J_2 = 1.9 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 165.9, 156.4, 154.7, 150.4, 143.2, 143.0, 131.0, 129.7, 124.0, 118.8, 111.3, 110.5, 107.8, 61.3, 60.9, 56.0. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{16}H_{14}ClNNaO_4S$ 374.0230, found 374.0229.

*2-(Benzo[d][1,3]dioxol-5-ylthio)benz[d]oxazole (**3l**).* **3l** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 10:90 to 15:85). White solid. Yield: 37% (50 mg). Mp: 83−85 °C. R_f (20% EtOAc/hexane): 0.25. IR (KBr, cm^{-1}): 1612, 1480, 1243, 930. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 (d, J = 7.2 Hz, 1H), 7.40 (d, J = 7.68 Hz, 1H), 7.27−7.20 (3H, m), 7.15 (s, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.04 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 164.0, 151.8, 149.6, 148.4, 141.9, 129.5, 124.3, 124.1, 118.9, 118.2, 115.0, 109.9, 109.2, 101.8. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{14}H_9NNaO_3S$ 294.0201, found 294.0204.

*2-((4-Methoxy-2,6-dimethylphenyl)thio)benz[d]oxazole (**3m**).* **3m** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). Yellow solid. Yield: 90% (65 mg). Mp: 62−64 °C. R_f (5% EtOAc/hexane): 0.5. IR (KBr, cm^{-1}): 1638, 1125, 1093, 1030. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57−7.55 (m, 1H), 7.39−7.37 (m, 1H), 7.24−7.20 (m, 2H), 6.77 (s, 2H), 3.82 (s, 3H), 2.49 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 163.8, 160.9, 151.8, 145.4, 142.2, 124.1, 123.7, 124.1, 118.7, 116.5, 114.2, 109.8, 55.1, 22.2. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{16}H_{15}NNaO_2S$ 308.0721, found 308.0724.

*2-((4-Methoxy-2,3-dimethylphenyl)thio)-5-methylbenz[d]oxazole (**3n**).* **3n** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97). faint yellow solid. Yield: 95% (71 mg). Mp: 120−123 °C. R_f (5% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1575, 1498, 1262, 1139, 1095. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm)

dx.doi.org/10.1021/jo501793q | J. Org. Chem. 2014, 79, 9655−9668

7.57 (d, J = 8.6 Hz, 1H), 7.36 (s, 1H), 7.25 (d, J = 7.0 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.86 (s, 3H), 2.42 (s, 3H), 2.40 (s, 3H), 2.2 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 164.4, 159.4, 150.1, 142.39, 142.36, 135.0, 133.9, 127.0, 124.7, 118.8, 117.0, 109.2, 108.5, 55.5, 21.6, 18.0, 12.7. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{17}H_{17}NNaO_2S$ 322.0878, found 322.0883.

*2-((4-Methoxy-2,3-dimethylphenyl)thio)-6-methylbenz[d]oxazole (**3o**).* **3o** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97). Faint yellow solid. Yield: 95% (71 mg). Mp: 110−112 °C. R_f (5% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}):1576, 1508, 1262, 1210, 1087. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.19 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 3.85 (m, 3H), 2.43 (s, 3H), 2.42 (s, 3H), 2.2 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 163.7, 159.3, 152.1, 142.3, 139.9, 134.9, 134.1, 127.0, 125.2, 118.2, 117.0, 110.2, 108.5, 55.5, 21.6, 18.0, 12.7. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{17}H_{17}NNaO_2S$ 322.0878, found 322.0877.

*2-((3,4-Dimethoxyphenyl)thio)naphth[2,3-d]oxazole (**3p**).* **3p** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 10:90). Orange solid. Yield: 52% (84 mg). Mp: 93−95 °C. R_f (20% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1582, 1506, 1496, 1377, 1259, 1230, 1130, 1003, 1011. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.43 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.63−7.49 (m, 3H), 7.34 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H), 7.26 (s, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.93−3.90 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 161.7, 150.6, 149.4, 149.3, 137.5, 131.0, 128.4, 127.9, 126.9, 125.7, 125.4, 125.2, 122.1,118.1, 117.4, 111.7, 110.4, 56.1, 56.0. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{19}H_{15}NNaO_3S$ (M^+ + Na): 360.0669, found 360.0670.

*2-((3,4-Dimethoxyphenyl)thio)benzo[d]thiazole (**3r**).* **3r** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 10:90 to 15:85). White solid. Yield: 28% (42 mg). Mp: 101−102 °C. R_f (20% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1582, 1502, 1426, 1255, 1235, 1135. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.86 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.41−7.33 (m, 2H), 7.27−7.21 (m, 2H), 6.95 (d, J = 8.2 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 154.0, 151.2, 149.7, 135.3, 129.1, 126.0, 124.1, 121.7, 120.7, 120.2, 118.1, 111.8, 56.0, 55.9. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{15}H_{13}NNaO_2S_2$ 326.0285, found 326.0282.

*2-((2,3,4-Trimethoxyphenyl)thio)benzo[d]thiazole (**3s**).* **3s** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 10:90). White solid. Yield: 52% (43 mg). Mp: 108−110 °C. R_f (10% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1455, 1424, 1294, 1088, 1004. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.85 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 8.7 Hz, 1H), 7.39 (dd, J_1= J_2= 7.7 Hz, 1H), 7.25 (dd, J_1 = $J_1$7= 0.9 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 171.3, 156.7, 155.2, 154.1, 143.2, 135.4, 132.3, 126.0, 124.0, 121.7, 120.7, 114.8, 107.9, 61.7, 61.0, 56.1. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{16}H_{15}NNaO_3S$ 356.0391, found 356.0415.

*5-Methyl-2-((4-(methylthio)phenyl)thio)benz[d]oxazole (**3t**).* **3t** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). White solid. Yield: 79% (57 mg). Mp: 69−70 °C. R_f (5% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1645, 1507, 1253,1147. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 (d, J = 8.3 Hz, 2H), 7.38 (s, 1H), 7.29−7.26 (m, 3H), 7.04 (d, J = 8.2 Hz, 1H), 2.51 (s, 3H), 2.42 (s, 3H) 3.83 (3H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 163.3, 150.1, 142.1, 141.7, 134.9, 134.2, 126.8, 125.2, 122.6, 119.0, 109.3, 21.4, 15.2. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{15}H_{13}NNaOS_2$ 310.0336, found 310.0336.

*5-Methyl-2-(methylthio)benz[d]oxazole (**3aa**, Table 1, Entry 21).*[26] Yellow liquid. Yield: 42% (19 mg). White semisolid. R_f (10% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1499, 1477, 1255, 1153. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.3855 (d, J = 0.6 Hz, 1H), 7.30−7.26 (m, 1H), 7.04−7.02 (m, 2H), 2.74 (s, 3H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 165.6, 150.2, 142.1, 134.0, 124.7, 118.3, 109.2, 21.4, 14.5. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_9H_{10}NOS$180.0483, found 180.0482.

*Reference Compound 5-Methylbenz[d]oxazol-2(3H)-one (**3bb**).*[27] White solid. Yield: 60% (8.94 g). Mp: 129−131 °C (lit.[28] 130−131 °C). R_f (10% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 2926, 1791, 1737, 1459, 1498. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.82 (br s, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.94−6.90 (m, 2H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 156.6, 141.9, 134.2, 129.4, 123.1, 110.7, 109.6, 21.4. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_8H_7NNaO_2$ 172.0372, found 172.0374.

*4-((5-Methylbenz[d]oxazol-2-yl)thio)phenol (**5a**).* **5a** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 5:95 to 15:85). White solid. Yield: 68% (44 mg). Mp: 185−186 °C. R_f (20% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 3233, 1588, 1491, 1460, 1230, 1153, 1091. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.30 (br s, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.36−7.34 (m, 2H), 7.08 (d, J = 8.2 Hz, 1H), 6.68 (d, J = 8.2 Hz, 2H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 167.6, 159.6, 150.0, 140.8, 137.2, 134.7, 125.4, 117.83, 117.80, 114.0, 109.55, 21.3. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{14}H_{12}NNaO_2S$ 258.0589, found 258.0590.

*4-((5-Chlorobenz[d]oxazol-2-yl)thio)phenol (**5b**).* **5b** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 5:95 to 15:85). Brown crystalline solid. Yield: 84% (58 mg). Mp: 190−192 °C. R_f (20% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 3437, 1618, 1460, 1286. ^1H NMR (400 MHz, DMSO): δ (ppm) 10.16 (br s, 1H), 7.69 (s, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.33−7.31 (m, 1H), 6.90 (d, J = 8.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ (ppm) 165.9, 159.7, 150.1, 142.7, 137.1, 128.9, 124.3, 118.3, 116.9, 113.3, 115.5. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{13}H_8NNaO_2SCl$ 299.9862, found 299.9863.

*4-(Benz[d]oxazol-2-ylthio)-2,6-dimethylphenol (**5c**).* **5c** was prepared as described in the typical experimental procedure. Pale yellow solid. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 5:95 to 10:90). Yield: 89% (60 mg). Mp: 210−212 °C. R_f (10% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 3413, 1649, 1507, 1452, 2452, 1320, 1257, 1204. ^1H NMR (400 MHz, DMSO): δ (ppm) 8.93 (s, 1H), 7.61−7.57 (m, 2H), 7.30−7.28 (m, 4H), 2.19 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ (ppm) 163.9, 155.6, 151.2, 141.4, 135.2, 126.0, 124.6, 124.4, 118.5, 113.6, 110.3, 16.4. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{15}H_{13}NNaO_2S$ 294.0565, found 294.0563.

*4-((5-Chlorobenz[d]oxazol-2-yl)thio)-2,6-dimethylphenol (**5d**).* **5d** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 10:90). Cream-colored solid. Yield: 79% (60 mg). Mp: 216−218 °C. R_f (10% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 3448, 1648, 1475, 1253, 1133. ^1H NMR (400 MHz, DMSO): δ (ppm) 8.95 (br s, 1H), 7.69 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.32−7.30 (m, 3H), 2.18 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ (ppm) 166.1, 155.8, 150.0, 142.7, 135.3, 128.8, 126.0, 124.2, 118.2, 113.0, 111.5, 16.4. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{15}H_{12}ClNNaO_2S$ 328.0175, found 328.0175.

*3,5-Dimethyl-4-((5-methylbenz[d]oxazol-2-yl)thio)phenol (**5e**).* **5e** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 10:90). White solid. Yield: 72% (52 mg). Mp: 248−250 °C. R_f (20% EtOAc/hexane): 0.3. IR (KBr, cm^{-1}): 3473, 3123, 2922, 1590, 1463, 1313, 1257, 1152, 1105, 1023. ^1H NMR (400 MHz, DMSO): δ (ppm) 10.07 (br, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.31 (s, 1H), 7.04 (d, J = 8.2 Hz, 1H), 6.67 (s, 2H), 2.32 (s, 3H), 2.29 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ (ppm) 163.6, 159.5, 149.9, 145.3, 141.9, 134.5, 125.5, 118.6, 116.1, 114.3, 109.9, 21.9, 21.2. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{16}H_{16}NO_2S$ 286.0902, found 286.0902.

*4-(Benz[d]oxazol-2-ylthio)-2,6-di-tert-butylphenol (**5f**).* **5f** was prepared as described in the typical experimental procedure. The

dx.doi.org/10.1021/jo501793q | J. Org. Chem. 2014, 79, 9655−9668

crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 5:95). Faint yellow solid. Yield: 82% (71 mg). Mp: 96−98 °C. R_f (10% EtOAc/hexane): 0.6. IR (KBr, cm^{-1}): 3448, 1615, 1451, 1223. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 (d, J = 7.4 Hz, 1H), 7.50 (s, 2H), 7.40 (d, J = 8.1 Hz, 1H), 7.25−7.20 (m, 2H), 5.50 (br s, 1H), 1.45 (s, 18H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 164.5, 155.6, 151.8, 142.2, 137.2, 132.0, 124.2, 123.9, 118.9, 116.0, 109.9, 34.5, 30.1. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{21}H_{26}NO_2S$ 356.1684, found 356.1684.

*2,6-Di-tert-butyl-4-((6-methylbenz[d]oxazol-2-yl)thio)phenol (**5g**).* **5g** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 2:98). Yellow solid. Yield: 77% (71 mg). Mp: 146−148 °C. R_f (5% EtOAc/hexane): 0.8. IR (KBr, cm^{-1}): 3432, 1641, 1504, 1260, 1213. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (s, 2H), 7.46 (d, J = 8.1 Hz, 1H), 7.21 (s, 1H), 7.06 (d, J = 8.0 Hz, 1H), 5.48 (br, 1H), 2.43 (s, 3H), 1.45 (s, 18H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 163.3, 155.5, 152.1, 139.9, 137.1, 134.3, 131.9, 125.3, 118.2, 116.3, 110.2, 34.5, 30.1, 21.6. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{22}H_{27}NNaO_2S$ 392.1660, found 392.1660.

*4-((5-Methylbenz[d]oxazol-2-yl)thio)benzene-1,2-diol (**5h**).* **5h** was prepared as described in the typical experimental procedure. White solid. Yield: 72% (49 mg). Mp: 208−210 °C. R_f (30% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 3507, 3468, 1596, 1507, 1492, 1479, 1281, 1257. ^1H NMR (400 MHz, DMSO): δ (ppm) 9.61(br s, 1H), 9.47 (br s, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.39 (s, 1H), 7.10−7.06 (m, 2H), 6.99 (dd, J_1 = 8.2 Hz, J_2 = 2 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ (ppm) 163.6, 149.5, 148.0, 146.2, 141.6, 134.0, 126.8, 125.3, 122.0, 118.4, 116.6, 113.8, 109.7, 20.9. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{14}H_{11}NNaO_3S$ 296.0357, found 296.0358.

*4-(Benz[d]oxazol-2-ylthio)benzene-1,2-diol (**5i**).*[6a] **5i** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 30:70). Cream-colored solid. Yield: 62% (80 mg). Mp: 158−160 °C (lit.[6a] 155−157 °C). R_f (30% EtOAc/hexane): 0.25. IR (KBr, cm^{-1}): 3537, 3450, 2924, 1597, 1508, 1497, 1454, 1334,1280, 1239, 1132, 1113. ^1H NMR (400 MHz, DMSO): δ (ppm) 9.57 (br s, 1H), 9.48 (br s, 1H), 7.62−7.59 (m, 2H), 7.31−7.30 (m, 2H), 7.08 (d, J = 2.0 Hz, 1H), 7.01 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1H), 6.87−6.86 (d, J = 8.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ(ppm) 163.7, 151.3, 148.0, 146.2, 141.4, 126.8, 124.6, 124.4, 122.1, 118.5, 116.6, 113.7, 110.2. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{13}H_9NNaO_3S$ 282.0201, found 282.0198.

*5-Methyl-2-(thiophene-2-ylthio)benz[d]oxazole (**7a**).* **7a** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). Colorless crystalline solid. Yield: 75% (92 mg). Mp: 85−87 °C. R_f (5% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1637, 1491, 1254, 1146. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (dd, J_1 =5.3 Hz, J_2 =0.8 Hz, 1H), 7.48−7.47 (m, 1H), 7.39 (s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.13 (dd, J_1 =5.3 Hz, J_2 =3.7 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 162.6, 150.2, 142.0, 137.7, 134.3, 133.0, 128.0, 125.4, 123.2, 119.2, 109.4, 21.4. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{12}H_9NNaOS_2$ 270.0023, found 270.0035.

*2-(Thiophene-2-ylthio)benz[d]oxazole (**7b**).* **7b** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). Colorless solid. Yield: 52% (60 mg). Mp: 85−87 °C. R_f (5% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1638, 1460, 1375. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63−7.60 (m, 2H), 7.49−7.48 (m, 1H), 7.22 (dd, J_1 = 6.6 Hz, J_2 = 1.9 Hz, 1H), 7.28−7.24 (m, 2H), 7.16−7.14 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 162.8, 151.9, 141.9, 137.8, 133.1, 128.1, 124.45, 124.38, 123.0, 119.2, 110.1. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{11}H_8NOS_2$234.0047, found 234.0048.

*5-Methyl-2-((5-methylthiophene-2-yl)thio)benz[d]oxazole (**7c**).* **7c** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). Dark brown liquid. Yield: 72% (94 mg). R_f (5% EtOAc/hexane): 0.5. IR (neat, cm^{-1}): 1781, 1498, 1479, 1256, 1145, 1100. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 740 (s, 1H), 7.29−7.26 (m, 2H), 7.04 (d, J = 8.3 Hz, 1H), 6.80 (d, J = 2.7 Hz, 1H), 2.54 (s, 3H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 163.1, 150.1, 148.1, 142.0, 138.1, 134.1, 126.4, 125.2, 119.6, 119.0, 109.4, 21.4, 15.8. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{13}H_{11}NNaOS_2$ 284.0182, found 284.0180.

*2-((5-Methylthiophene-2-yl)thio)benz[d]oxazole (**7d**).* **7d** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). Dark brown liquid. Yield: 80% (50 mg). R_f (5% EtOAc/hexane): 0.45. IR (neat, cm^{-1}): 1783, 1498, 1451, 1238, 1127. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 (dd, J_1 = 6.7 Hz, J_2 = 2.0 Hz, 1H), 7.41 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 1H), 7.27−7.20 (m, 3H), 6.79 (d, J = 2.7 Hz, 1H), 2.53 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 163.3, 151.9, 148.3, 141.9, 138.2, 126.4, 124.3, 124.2, 119.5, 119.1, 110.0, 15.9. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{12}H_9NNaOS_2$ (M^+ + Na): 270.0023, found 270.0023.

*2-((2,5-Dimethylthiophene-3-yl)thio)-5-methylbenz[d]oxazole (**7e**).* **7e** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). Dark brown liquid. Yield: 74% (102 mg). R_f (5% EtOAc/hexane): 0.6. IR (KBr, cm^{-1}): 1503, 1479, 1255, 1144, 1100. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.4 (s, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.02 (dd, J_1 = 8.3 Hz, J_2 = 1.1 Hz, 1H), 6.78 (d, J = 0.9 Hz, 1H), 2.48 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 163.1, 150.1, 143.6, 142.2, 136.6, 134.0, 129.8, 124.9, 118.9, 116.8, 109.3, 21.4, 15.3, 14.2. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{14}H_{13}NNaOS_2$ 298.0336, found 298.0340.

*2-(Benzo[b]thiophene-3-ylthio)-5-methylbenz[d]oxazole (**7f**).* **7f** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97). Yellow solid. Yield: 72% (54 mg). Mp: 96−98 °C. R_f (5% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1503, 1477, 1252, 1143, 1099. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.0 (s, 1H), 7.92−7.86 (m, 2H), 7.43−7.41 (m, 2H), 7.35 (s, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 161.9, 150.1, 142.1, 139.6, 138.8, 134.8, 134.3, 125.3, 125.2, 125.1, 122.9, 122.7, 119.0, 117.2, 109.4, 21.4. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{16}H_{11}NNaOS_2$ 320.0180, found 320.0179.

*2-(Benzo[b]thiophene-3-ylthio)benz[d]oxazole (**7g**).* **7g** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). yellow solid. Yield: 61% (87 mg). Mp: 128−129 °C. R_f (5% EtOAc/hexane): 0.5. IR (KBr, cm^{-1}): 1633, 1502, 1453, 1238, 1127. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01 (s, 1H), 7.93−7.87 (m, 2H), 7.56 (d, J = 7.2 Hz, 1H) 7.43−7.40 (m, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.24−7.18 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 162.1, 151.8, 141.9, 139.6, 138.8, 135.0, 125.2, 125.1, 124.4, 124.2, 123.0, 122.7, 119.0, 117.0, 110.0. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{15}H_9NNaO_2S_2$ 306.0025, found 306.0023.

*2-(Benzo[b]thiophene-3-ylthio)naphth[2,3-d]oxazole (**7h**).* **7h** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 3:97 to 5:95). Cream-colored solid. Yield: 23% (19 mg). Mp: 137−139 °C. R_f (5% EtOAc/hexane): 0.5. IR (KBr, cm^{-1}): 1636, 1457, 1383, 1374, 1142. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.41 (d, J = 8.2 Hz, 1H), 8.05 (s, 1H), 7.96−7.98 (m, 3H), 7.67 (d, J = 8.9 Hz, 1H), 7.60 (dd, J_1 = J_2 = 7.3 Hz, 1H), 7.52−7.47 (m, 2H), 7.45−7.42 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 159.9, 149.3, 139.6, 138.9, 137.4, 134.5, 131.0, 128.4, 127.0, 125.7, 125.4, 125.3, 125.2, 125.1, 122.9, 122.8, 122.1, 117.7, 110.4. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{19}H_{11}NNaOS_2$ 356.0180, found 356.0182.

*2-((2,5-Dimethoxyphenyl)thio)-5-methylbenz[d]oxazole (**9**).* **9** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 5:95 to 10:90). White solid. Yield: 38% (57 mg). Mp: 116−118 °C. R_f (10% EtOAc/hexane): 0.4. IR (KBr, cm^{-1}): 1499, 1480, 1278, 1224, 1142. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 (s, 1H), 7.26

dx.doi.org/10.1021/jo501793q | J. Org. Chem. 2014, 79, 9655−9668

(d, J = 8.0 Hz, 1H), 7.23 (d, J = 2.9 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.98 (dd, J_1 = 9.0 Hz, J_2 = 2.9 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 162.7, 153.6, 153.4, 150.1, 142.3, 134.0, 125.1, 120.5, 119.0, 116.9, 116.3, 112.8, 109.3, 56.7, 55.8, 21.4. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{16}H_{15}NNaO_3S$ 324.0670, found 324.0670.

*5-Methyl-2-((2,4,6-trimethoxyphenyl)thio)benz[d]oxazole (**10a**).* **10a** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 20:80). White solid. Yield: 80% (66 mg). Mp: 164−166 °C. R_f (20% EtOAc/hexane): 0.5. IR (KBr, cm^{-1}): 1600, 1583, 1493, 1234, 1148, 1126. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (s, 1H), 7.22 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.98 (s, 2H), 3.87 (s, 3H), 3.81 (s, 6H), 2.4 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 164.3, 163.6, 162.0, 150.1, 142.6, 133.6, 124.3, 118.6, 109.1, 94.1, 91.4, 56.3, 55.4, 21.4. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{17}H_{17}NNaO_4S$ 354.0776, found 354.0776.

*6-Nitro-2-((2,4,6-trimethoxyphenyl)thio)benz[d]oxazole (**10b**).* **10b** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 20:80). Faint yellow solid. Yield: 81% (73 mg). Mp: 164−166 °C. R_f (20% EtOAc/hexane): 0.2. IR (KBr, cm^{-1}): 1594, 1489, 1339, 1232, 1113. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.26 (d, J = 1.9 Hz, 1H), 8.20 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 6.24 (s, 2H), 3.89 (s, 3H), 3.84 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 170.8, 164.3, 162.0, 150.8, 147.9, 143.8, 120.5, 117.9, 106.1, 92.3, 91.4, 56.3, 55.5. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{16}H_{14}N_2NaO_6S$ 385.0470, found 385.0469.

*2-((2,4,6-Trimethoxyphenyl)thio)benzo[d]thiazole (**11a**).*[5e] **11a** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 10:90 to 15:85). White solid. Yield: 33% (55 mg). Mp: 120−122 °C (lit.[5e] 88−89 °C). R_f (20% EtOAc/hexane): 0.3. IR (KBr, cm^{-1}): 1597, 1581, 1454, 1426, 1230,1123. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.83 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 7.6 Hz, 1H), 7.35 (dd, J_1 = J_2 = 7.5 Hz, 1H), 7.20 (dd, J_1 = J_2 = 7.5 Hz, 1H), 6.23 (s, 2H), 3.90 (s, 3H), 3.84 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 172.8, 164.3, 162.5, 154.6, 135.3, 125.7, 123.5, 121.4, 120.5, 97.2, 91.1, 56.3, 55.5. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{16}H_{15}NNaO_3S_2$ 356.0391, found356.0391.

*2,2′-((2,4,6-Trimethoxy-1,3-phenylene)bis(sulfanediyl))bis(benzo-[d]thiazole) (**11b**).* **11b** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 20:80). White solid. Yield: 33% (41 mg). Mp: 178−180 °C. R_f (20% EtOAc/hexane): 0.2. IR (KBr, cm^{-1}): 1575, 1422, 1376, 1217, 1119. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.92 (d, J = 7.8 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.43 (dd, J_1 = J_2 = 7.5 Hz, 2H), 7.31 (dd, J_1 = J_2 = 7.5 Hz, 2H), 6.94 (s, 1H), 3.99 (s, 6H), 3.82 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 170.2, 165.7, 165.0, 153.8, 134.7, 126.4, 124.2, 121.7, 121.2, 103.6, 94.5, 63.1, 57.3. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{23}H_{18}N_2$ NaO_3S_4 521.0092, found 521.0098.

*2-(Mesitylthio)-5-methylbenz[d]oxazole (**13**).* **13** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (eluent hexane). Colorless crystalline solid. Yield: 71% (50 mg). Mp: 117−119 °C. R_f (3% EtOAc/hexane): 0.3. IR (KBr, cm^{-1}): 1565, 1496, 1477, 1255, 1143, 1100. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 (s, 1H), 7.25 (d, J = 10.3 Hz, 1H), 7.04 (s, 2H), 7.01 (d, J = 8.4 Hz, 1H), 2.46 (s, 6H), 2.40 (s, 3H), 2.33 (s, 3H). $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$): δ (ppm) 163.4, 150.1, 143.5, 142.3, 140.6, 134.0, 129.6, 124.7, 122.4, 118.8, 109.2, 21.9, 21.4, 21.2.. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{17}H_{17}NNaOS$ 306.0929, found 306.0931.

*2-Methoxy-4-((5-methylbenz[d]oxazol-2-yl)thio)phenol (**15**).* **15** was prepared as described in the typical experimental procedure. The crude product was purified on a silica gel (100−200 mesh) column (EtOAc/hexane, 20:80). Colorless crystalline solid. Yield: 87% (124.5 mg). Mp: 184−186 °C. R_f (20% EtOAc/hexane): 0.3. IR (KBr, cm^{-1}): 3434, 1595, 1491, 1267, 1234, 1147, 1101. ^1H NMR (400 MHz, DMSO): δ (ppm) 7.47 (d, J = 8.2 Hz, 1H), 7.39 (s, 1H), 7.26 (s, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 3.78 (s, 3H), 2.36 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ (ppm) 163.6, 149.5, 149.0, 148.3, 141.7, 134.0, 128.7, 125.2, 118.7, 118.4, 116.4, 114.0, 109.7, 55.8, 20.9. HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{15}H_{13}NNaO_3S$ 310.0514, found 310.0524.

*Bis(benzo[d]thiazol-2-yl)sulfane (**17**).*[29] White solid. Yield: 27% (81 mg). Mp: 101−102 °C (lit.[28] 103−104 °C). R_f (10% EtOAc/hexane): 0.5. IR (KBr, cm^{-1}): 2364, 1636, 1410, 1237, 1010, 991, 754. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.04 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 7.8 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 159.9, 152.8, 136.5, 126.6, 125.6, 122.9, 121.2. MS (m/z): 300 (M^+).

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C spectra and spectral data for all compounds, plausible mechanisms for the formation of **3aa** and **16**, ORTEP diagrams and crystallographic data for **7a**, **7g**, and **15**, and CIF data for **7a**, **7g**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: prabhu@orgchem.iisc.ernet.in. Phone: +91-80-22932887. Fax: +91-80-23600529.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Prof. P. Balaram on the occasion of his 65th birthday. Financial support from IISc CSIR, New Delhi (Grant 01(2415)/10/EMR-II), and RL Fine Chem is gratefully acknowledged. We thank Prof. T. N. Guru Row, Mr. M. S. Pavan, and Mr. A. Hosamani for their help with the X-ray crystal structure determination and Dr. A. R. Ramesha for useful discussion. B.V.V. thanks CSIR for a senior fellowship.

■ REFERENCES

(1) (a) Gangjee, A.; Zeng, Y.; Talreja, T.; McGuire, J. J.; Kisliuk, R. L.; Queener, S. F. *J. Med. Chem.* **2007**, *50*, 3046. (b) De Martino, G.; Edler, M. C.; La Regina, G.; Coluccia, A.; Barbera, M. C.; Barrow, D.; Nicholson, R. I.; Chiosis, G.; Brancale, A.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 947−954. (C) Sciabola, S.; Carosati, E.; Baroni, M.; Mannhold, R. *J. Med. Chem.* **2005**, *48*, 3756. (d) Pasquini, S.; Mugnaini, C.; Tintori, C.; Botta, M.; Trejos, A.; Arvela, R. K.; Larhed, M.; Witvrouw, M.; Michiels, M.; Christ, F.; Debyser, Z.; Corelli, F. *J. Med. Chem.* **2008**, *51*, 5125. (e) Sun, Z.-Y.; Botros, E.; Su, A.-D.; Kim, Y.; Wang, E.; Baturay, N. Z.; Kwon, C.-H. *J. Med. Chem.* **2000**, *43*, 4160−4168.

(2) (a) Massari, S.; Daelemans, D.; Barreca, M. L.; Knezevich, A.; Sabatini, S.; Cecchetti, V.; Marcello, A.; Pannecouque, C.; Tabarrini, O. *J. Med. Chem.* **2010**, *53*, 641. (b) Choudhary, A. N.; Kumar, A.; Jural, V. *Mini-Rev. Med. Chem.* **2010**, *10*, 705. (c) Itai, A.; Muto, S.; Tokuyama, R.; Fukazawa, H.; Ohara, T.; Kato, T. WO 2007023882, 2007. (d) Renee, N. B.; Rachel, C.; David, K. C.; Stephanie, H.; Angela, L.; Guy, Y. K.; Darryl, B. M.; Roland, N.; Pauline, C. S.; Simon, P. T.; Watson, K. G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2051. (e) Black, L. A.; Cowart, M. D.; Gfesser, G. A.; Wakefield, B. D.; Altenbach, R. J.; Liu, H.; Zhao, C.; Hsieh, G. C. WO 2009085945, 2009. (f) Paramashivappa, R.; Kumar, P. P.; Rao, P. V. S.; Rao, A. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 657. (g) Kumar, R. V.; Kumar, K. V. S. R. S.; Gopal, K. R. *J. Heterocycl. Chem.* **2005**, *42*, 153. (h) Tehim, A.; Herbert, B.; Nguyen, T. M.; Xie, W.; Gauss, C. M. WO 2004029050, 2004.

(3) (a) Greco, M. N.; Hageman, W. E.; Powell, E. T.; Tighe, J. J.; Persico, F. J. *J. Med. Chem.* **1992**, *35*, 3180. (b) Zhang, J.-T.; Qi, J.; Feng, H.; Dong, Z. WO2010048603, 2010. (c) Greco, M. N.; Hageman, W. E.;

Powell, E. T.; Tighe, J. J.; Persico, F. J. *J. Med. Chem.* **1992**, *35*, 3180. (d) Barchuk, W. T.; Dunford, P. J.; Edwards, J. P.; Fourie, A. M.; Karlsson, L.; Quan, J. M. US2008194630. (e) Koci, J.; Klimesova, V.; Waisser, K.; Kaustova, J.; Dahse, H.-M.; Moellmann, U. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3275. (f) Waisser, K.; Sidoova, E.; Odlerova, Z.; Goeckeritz, W.; Drsata, J. *Pharmazie* **1987**, *42*, 536. (g) Naya, A.; Kobayashi, K.; Ishikawa, M.; Ohwaki, K.; Saeki, T.; Noguchi, K.; Ohtake, N. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1219. (h) Dumas, J.; Brittelli, D.; Chen, J.; Dixon, B.; Hatoum-Mokdad, H.; Konig, G.; Sibley, R.; Witowsky, J.; Wong, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2531. (i) Wei, H.; Yang, G.-F. *Bioorg. Med. Chem.* **2006**, *14*, 8280. (j) Yonova, I. M.; Osborne, C. A.; Morrissette, N. S.; Jarvo, E. R. *J. Org. Chem.* **2014**, *79*, 1947.

(4) (a) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880. (b) Fernández-Rodríguez, M. A.; Hartwig, J. F. *Chem.—Eur. J.* **2010**, *16*, 2355. (c) Xu, H.-J.; Liang, Y.-F.; Zhou, X.-F.; Feng, Y.-S. *Org. Biomol. Chem.* **2012**, *10*, 2562. (d) He, G.; Huang, Y.; Tong, Y.; Zhang, J.; Zhao, D.; Zhou, S.; Han, S. *Tetrahedron Lett.* **2013**, *54*, 5318. (e) Didenko, A. V.; Labeish, V. V.; Trikhin, A. V.; Petrov, M. L. *Russ. J. Org. Chem.* **2007**, *43*, 1092. (f) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309. (g) Kuroda, K.; Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* **2008**, *37*, 592. (h) McCrea-Hendrick, M.; Nichols, C. J. *Synth. Commun.* **2009**, *39*, 3611.

(5) (a) Arisawa, M.; Toriyama, F.; Yamaguchi, M. *Tetrahedron Lett.* **2011**, *52*, 2344. (b) Zhou, A.-X.; Liu, X.-Y.; Yang, K.; Zhao, S.-C.; Liang, Y.-M. *Org. Biomol. Chem.* **2011**, *9*, 5456. (c) Inomata, H.; Toh, A.; Mitsui, T.; Fukuzawa, S.-i. *Tetrahedron Lett.* **2013**, *54*, 4729. (d) Fukuzawa, S.-i.; Shimizu, E.; Atsuumi, Y.; Haga, M.; Ogata, K. *Tetrahedron Lett.* **2009**, *50*, 2374. (e) Zhang, S.; Qian, P.; Zhang, M.; Hu, M.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 6732. (f) Zhang, M.; Zhang, S.; Pan, C.; Chen, F. *Synth. Commun.* **2011**, *42*, 2844. (g) Prasad, C. D.; Balkrishna, S. J.; Kumar, A.; Bhakuni, B. S.; Shrimali, K.; Biswas, S.; Kumar, S. *J. Org. Chem.* **2013**, *78*, 1434.

(6) (a) Mohsen, H. T. A.; Conrad, J.; Beifuss, U. *Green Chem.* **2014**, *16*, 90. (b) H.Davarani, S. S.; Ramyar, S.; Masoumi, L.; Fumani, N. S.; Moghaddam, A. B. *J. Electrochem. Soc.* **2008**, *155*, E120. (c) Amani, A.; Nematollahi, D. *J. Org. Chem.* **2012**, *77*, 11302−11306. (d) Nematollahi, D.; Tammari, E. *J. Org. Chem.* **2005**, *70*, 7769. (e) Tammari, E.; Mirazi, N.; Nematollahi, D. *Mendeleev Commun.* **2006**, *16*, 285.

(7) (a) Shi, L.; Liu, X.; Zhang, H.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2011**, *76*, 4200. (b) Murru, S.; Mondal, P.; Yella, R.; Patel, B. K. *Eur. J. Org. Chem.* **2009**, 5406.

(8) (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (c) Haibach, M. C.; Seidel, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 5010. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.

(9) (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (e) Li, C.-J. *Acc. Chem. Res.* **2008**, *42*, 335.

(10) Kondo, T.; Mitsudo, T.-a. *Chem. Rev.* **2000**, *100*, 3205.

(11) (a) Alagiri, K.; Kumara, G. S. R.; Prabhu, K. R. *Chem. Commun.* **2011**, *47*, 11787−11789. (b) Alagiri, K.; Prabhu, K. R. *Org. Biomol. Chem.* **2012**, *10*, 835. (c) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092.

(12) Kamat, M. N.; Rath, N. P.; Demchenko, A. V. J. *Org. Chem.* **2007**, *72*, 6938.

(13) (a) Jordan, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. *Med. Res. Rev.* **1998**, *18*, 259. (b) De Martino, G.; La Regina, G.; Coluccia, A.; Edler, M. C.; Barbera, M. C.; Brancale, A.; Wilcox, E.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2004**, *47*, 6120.

(14) Alcaraz, M.-L.; Atkinson, S.; Cornwall, P.; Foster, A. C.; Gill, D. M.; Humphries, L. A.; Keegan, P. S.; Kemp, R.; Merifield, E.; Nixon, R. A.; Noble, A. J.; O'Beirne, D.; Patel, Z. M.; Perkins, J.; Rowan, P.; Sadler, P.; Singleton, J. T.; Tornos, J.; Watts, A. J.; Woodland, I. A. *Org. Process Res. Dev.* **2005**, *9*, 555.

(15) Although the reaction of **1a** and **2a** in the presence of TEMPO has resulted in the formation of **3a** in low yield (60%), we could not observe the formation of the corresponding TEMPO adduct as the reaction mixture was a complex mixture of products.

(16) Mavrova, A. Ts.; Anichina, K. K.; Vuchev, D. I.; Tsenov, J. A.; Kondevad, M. S.; Micheva, M. K. *Bioorg. Med. Chem.* **2005**, *13*, 5550.

(17) Under optimal reaction conditions, the reaction of phenol (94 mg, 1 mmol) with 5-methylbenz[*d*]oxazole-2(3*H*)-thione (41.25 mg, 0.25 mmol) furnished the product **5a** (44 mg, 68%).

(18) Under similar reaction conditions, 4 equiv of benzothiophene derivatives was used.

(19) Singh, M. S.; Singh, P.; Singh, S. *Indian J. Chem.* **2007**, *46B*, 1666.

(20) Lok, R.; Leone, R. E.; Williams, A. J. *J. Org. Chem.* **1996**, *61*, 3289.

(21) Harizi, A.; Romdhane, A.; Mighri, Z. *Tetrahedron Lett.* **2000**, *41*, 5833.

(22) Nagano, T.; Itoh, M.; Matsumura, K. *J. Am. Chem. Soc.* **1953**, *75*, 2770.

(23) Katz, L.; Cohen, M. *J. Org. Chem.* **1954**, *19*, 758.

(24) Roger, S.; Marie, C. A.; Philip, C.; Miao, D.; Susan, J.; Derek, L.; Stephen, O.; Ning, S.; Gan, W.; Mingbao, Z.; Lei, Z. US2004224997 (A1), 2004.

(25) Jacobson, P. *Chem. Ber.* **1888**, *21*, 415.

(26) Peter, G.; David,S. M.; John, H. A.; Mark,H. US2009082359 (A1), 2009.

(27) Masakuni, K.; Hideyuki, O.; Tetsuya, T.; Masashi, T.; Masaki, S.; Takehiro, H. US2011039893 (A1), 2011.

(28) Wang, X.; Ling, G.; Xue, Y.; Lu, S. *Eur. J. Org. Chem.* **2005**, 1675.

(29) Arisawa, M.; Ichikawa, T.; Yamaguchi, M. *Org. Lett.* **2012**, *14*, 5318.