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PAPER

Copper-catalyzed direct thiolation of azoles with aliphatic thiols†

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Cu(II)-catalyzed direct thiolation of azoles with thiols is described *via* intermolecular C–S bond formation/C–H functionalization under oxidative conditions. Both aryl thiols and aliphatic thiols are used as coupling partners, and furnished the thiolation products in moderate to good yields. The reaction is compatible with a wide range of heterocycles including oxazole, thiazole, imidazole and oxadiazole.

Introduction

Transition-metal-catalyzed C–S bond formation has been a subject of intense study due to the importance of aryl sulfides, aliphatic-heteroaromatic sulfides and their derivatives in numerous biological and pharmaceutically active compounds.[1] In the past decade, the transition-metal-catalyzed cross-coupling reactions of ArX (X = Cl, Br, I, OTf and $B(OH)_2$) with sulfur nucleophiles, such as, aryl thiols, aliphatic thiols and diaryl disulfides, are powerful tools for the formation of C–S bonds.[2]

In contrast, with the increasing requirements for environmentally benign and atom economic processes, the transition-metal-catalyzed C–H functionalization has received substantial attention in recent years, as a potentially more efficient and complementary process to the conventional cross-coupling methodology. However, in this aforementioned class of reactions, much effort has been paid on C–C and C–hetero bonds. The formation of a C–S bond *via* transition-metal-catalyzed C–H activation was not realized until Yu and co-workers first reported the thiolation of 2-phenylpyridine with PhSH and MeSSMe using $Cu(OAc)_2$ as a catalyst under oxygen atmosphere.[3] Recently, Dong and co-workers described the Pd-catalyzed direct sulfonylation of a 2-phenylpyridine C–H bond with $ArSO_2Cl$.[4] Very recently, Qing described a Cu(II)-mediated reaction of an aryl C–H bond with DMSO for *ortho*-substituted methylthiolation.[5] Meanwhile, Cheng reported CuI-catalyzed thiolation of the di- or trimethoxyl- benzene arene C–H bond with ArSSAr.[6] Besides the aforementioned aromatic C–S bond formation, the related counterparts on heterocycles were also revealed. Doi and Batey independently illustrated Pd-catalyzed reactions to produce 2-substituted benzothiazoles through C–H functionalization/intramolecular C–S bond formation.[7] Subsequently, Li and co-workers disclosed iron-catalyzed sulfenylation of an indole C–H bond with diaryl disulfides, with a catalytic amount of iodine supplied to promote the reaction.[8] Additionally, Fukuzawa and co-workers demonstrated a copper-catalyzed direct thiolation of a benzoxazole C–H bond with diaryl disulfides and aryl thiols.[9]

The direct arylation,[10] alkenylation[11] and amination[12] of heterocycles through the transition-metal-catalyzed C–H functionalization has been developed considerably. However, only one example of the formation of a C–S bond through the analogous reaction has been reported,[9] and the application of aliphatic thiols in the reaction of direct C–H functionalization/intermolecular C–S bond formation is still unexplored. These drawbacks have limited this reaction which prepares sulfides with biological activity or sulfides that lead to biologically active compounds. Thus, further development for direct C–H thiolation is strongly desired. Herein, we report an efficient copper-catalyzed direct thiolation of azoles with aliphatic thiols.

Results and discussion

Our initial efforts focused on the direct thiolation of benzoxazole (**1a**) (0.4 mmol) with 1-dodecanethiol (**2a**) (0.6 mmol) by using a stoichiometric amount of $Cu(OAc)_2 \cdot H_2O$ (2.2 equiv.) in DMSO under air atmosphere; the desired product was obtained in 27% isolated yield in 8 h (Table 1, entry 1). Encouraged by this preliminary result, we further investigated the reaction parameters and found that toluene was a better reaction medium than other solvents such as DMSO, DMF, xylene and dioxane (Table 1, entries 2–5). However, the desired cross-coupling was not observed when the amount of $Cu(OAc)_2 \cdot H_2O$ was reduced to 20 mol% (Table 1, entry 6). We hypothesized that stoichiometric amounts of copper were needed because it was consumed as a base and an oxidant. With use of 20 mol% of $Cu(OAc)_2 \cdot H_2O$ in the presence of 2.0 equiv. Cs_2CO_3 or K_2CO_3 (Table 1, entries 7–8), the reaction under O_2 resulted in trace yield of **3a**. Thus, further reactions with catalytic amounts of $Cu(OAc)_2 \cdot H_2O$ were conducted in the presence of metal salts as a base and an oxidant including all kinds of copper and silver salts, and these experiments showed that reactions conducted with CuO as the additive formed the cross-coupling product **3a** in excellent yield (Table 1, entry 9). When O_2 was employed (1 atm) instead of air under the optimized conditions, the yield of **3a** dropped to 50% (Table 1, entry 10). A

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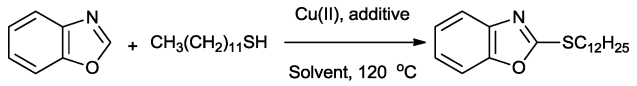
† Electronic supplementary information (ESI) available: ^1H NMR and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/c1ob05395g

Table 1 Optimization of the Reaction Conditions[a]



1a 2a 3a

Entry	Catalyst	Additive	Solvent	Yield[b] (%)
1	$Cu(OAc)_2{\cdot}H_2O$	$Cu(OAc)_2{\cdot}H_2O$	DMSO	27
2	$Cu(OAc)_2{\cdot}H_2O$	$Cu(OAc)_2{\cdot}H_2O$	DMF	38
3	$Cu(OAc)_2{\cdot}H_2O$	$Cu(OAc)_2{\cdot}H_2O$	xylene	35
4	$Cu(OAc)_2{\cdot}H_2O$	$Cu(OAc)_2{\cdot}H_2O$	dioxane	37
5	$Cu(OAc)_2{\cdot}H_2O$	$Cu(OAc)_2{\cdot}H_2O$	toluene	48
6	$Cu(OAc)_2{\cdot}H_2O$	—	toluene	0
7[c]	$Cu(OAc)_2{\cdot}H_2O$	Cs_2CO_3	toluene	trace
8[c]	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	toluene	trace
9	**$Cu(OAc)_2{\cdot}H_2O$**	**CuO**	**toluene**	**86**
10[c]	$Cu(OAc)_2{\cdot}H_2O$	CuO	toluene	50
11	$Cu(OAc)_2{\cdot}H_2O$	$Cu(OH)_2CO_3$	toluene	73
12	$Cu(OAc)_2{\cdot}H_2O$	$Cu(OH)_2$	toluene	38
13	$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3	toluene	53
14	$Cu(OAc)_2{\cdot}H_2O$	Ag_2O	toluene	36
15	$Cu(OAc)_2{\cdot}H_2O$	AgOAc	toluene	trace
16	$Cu(OAc)_2{\cdot}H_2O$	$AgNO_3$	toluene	0
17	$Cu(OAc)_2{\cdot}H_2O$	AgI	toluene	0
18	CuO	CuO	toluene	17
19[d]	$Cu(OAc)_2{\cdot}H_2O$	CuO	toluene	52

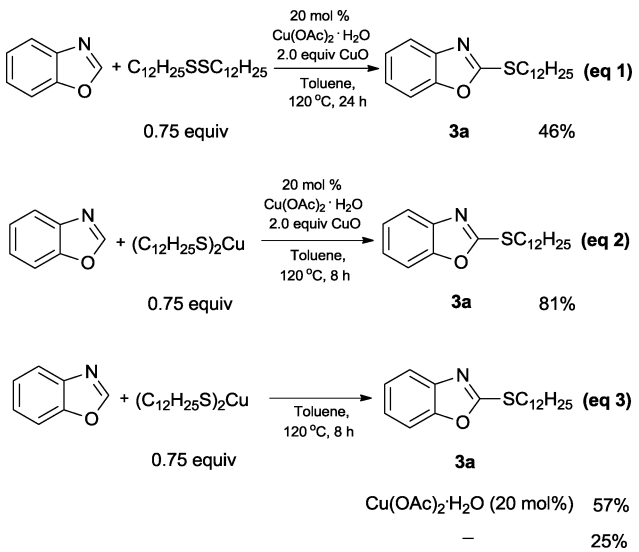
[a] **1a** (0.4 mmol), dodecanethiol **2a** (0.6 mmol), Cu(II) (20 mol%), additive (2.0 equiv.), dry solvent (2 mL), under air, 120 °C, 8 h. [b] Isolated yields. [c] Under O_2 atmosphere. [d] $Cu(OAc)_2{\cdot}H_2O$ (10 mol%).

comparable reaction efficiency was presented by $Cu(OH)_2CO_3$, while $Cu(OH)_2$, Ag_2CO_3 and Ag_2O showed lower reactivity (Table 1, entries 11–14). Other silver species, such as AgOAc, $AgNO_3$ and AgI were ineffective for this reaction (Table 1, entries 15–17). Notably, with the use of CuO instead of $Cu(OAc)_2{\cdot}H_2O$ as the catalyst, the desired product was isolated in only 17% yield under the same reaction conditions (Table 1, entry 18). Along with reducing the amount of catalyst by 10 mol%, the yield decreased to 52% (Table 1, entry 19).

Under the optimized conditions, the substrate scope towards this thiolation reaction was further investigated. A wide array of heterocycle compounds **1** were tested in the reaction with 1-dodecanethiol (**2a**), and the results are listed in Table 2. Benzoxazoles bearing substituents with diverse electronic properties, such as electron donation (methyl, methoxy groups) and slight electron deficiency (chloro derivative), all showed the better reactivity and furnished the products in moderate to good yields (Table 2, entries 2–4). However, a low yield was obtained in the case of 5-nitrobenzoxazole (Table 2, entry 5), which was deactivated by the strongly electron withdrawing nitro group. Various azoles, such as oxazoles, thiazoles and imidazoles, all smoothly reacted with **2a** to afford the desired products in good yields (Table 2, entries 6–13). Moreover, 2-phenyl-1,3,4-oxadiazole is a good coupling partner, and the desired corresponding product **3n** was obtained in moderate yield (Table 2, entry 14).

The Cu-catalyzed thiolation of azoles with various thiols was also investigated. Primary aliphatic thiols, whether short, medium or long chain, were engaged in the system, the desired corresponding products were obtained in moderate to good yields (Table 3, entries 1, 2, 6–10). Moreover, secondary aliphatic thiols, such as 2-propanethiol (**2d**) and cyclohexylmercaptan (**2e**), were used in this reaction, which produced the corresponding product **3q** and **3r** in 63% and 69% yield, respectively (Table 3, entries 3 and 4). However, when 2-methylpropane-2-thiol (**2f**) was reacted with benzoxazole (**1a**), the thiolation product **3s** was isolated only in 4% yield even with a prolonged reaction time of 24 h (Table 3, entry 5). These results indicated that the steric hindrance factors of the thiols play a key role in controlling the reactivity. We were also interested in extending the direct thiolation of azoles to aryl thiols. Benzoxazole, benzothiazole and 1-methylimidazole all smoothly reacted with benzenethiol (**2k**) to afford the desired products in low to moderate yields (Table 3, entries 11–13).

A mechanism analogous to those proposed for similar copper-catalyzed processes involving thiol copper species might be applicable to this thiolation procedure.[6,9] To investigate the reaction mechanism, the thiolations of benzoxazole with dodecyl disulfide and bis(dodecylthio)copper ($(C_{12}H_{25}S)_2Cu$) were studied, respectively. When dodecyl disulfide was used as the reaction partner, the product **3a** was obtained in 46% yield under the optimized conditions for 24 h (Scheme 1, eq 1). On the other hand, the reaction of benzoxazole and $(C_{12}H_{25}S)_2Cu$ under the same conditions for 8 h produced **3a** in 81% yield (Scheme 1, eq 2). Moreover, in the absence of CuO, the reaction yield was decreased to 57%, while in the absence of both CuO and $Cu(OAc)_2{\cdot}H_2O$, the yield was further decreased to 25% (Scheme 1, eq 3). These results indicated the importance of the formation of $(C_{12}H_{25}S)_2Cu$ as a key intermediate, which might be obtained more quickly from the reaction of the copper salt with a thiol than from the corresponding disulfide under these reaction conditions. Therefore, a plausible mechanism is proposed. The key intermediate $(RS)_2Cu$ would be firstly formed in the presence of a thiol and the copper salt. It reacts with benzoxazole (**1a**) to produce the corresponding ArCuSPh intermediate, which can then undergo reductive elimination to afford the product **3a**. Finally, the Cu(II) catalyst is regenerated by the oxidant.

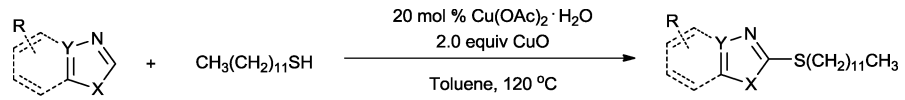


Scheme 1 Preliminary mechanism study.

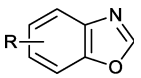
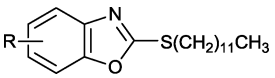
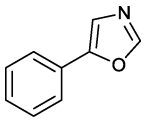
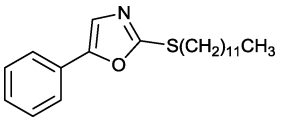
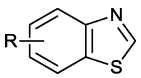
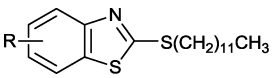
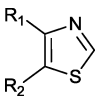
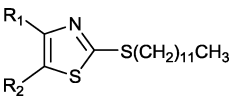
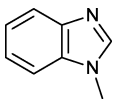
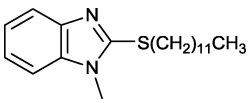
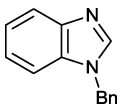
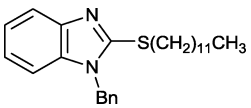
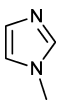
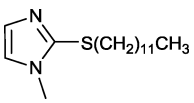
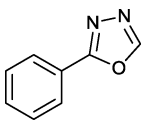
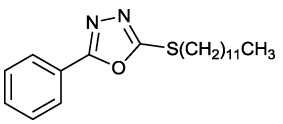
Conclusions

In conclusion, we have disclosed an efficient C–H functionalization/intermolecular C–S bond formation process. Various

Table 2 Reactions of **2a** with various heterocycles[a]



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

Entry	Heterocycle	1	Product	3	Yield[b] (%)
1		**1a** (R = H)		**3a** (R = H)	86
2		**1b** (R = 5-Me)		**3b** (R = 5-Me)	84
3		**1c** (R = 5-OMe)		**3c** (R = 5-OMe)	63
4		**1d** (R = 6-Cl)		**3d** (R = 6-Cl)	67
5		**1e** (R = 5-NO_2)		**3e** (R = 5-NO_2)	11
6		**1f**		**3f**	63
7		**1g** (R = H)		**3g** (R = H)	82
8		**1h**(R = 6-Me)		**3h** (R = 6-Me)	84
9		**1i** (R_1, R_2 = H)		**3i** (R_1, R_2 = H)	83
10		**1j** (R_1, R_2 = Me)		**3j** (R_1, R_2 = Me)	89
11		**1k**		**3k**	70
12		**1l**		**3l**	69
13		**1m**		**3m**	73
14		**1n**		**3n**	50

[a] **1** (0.4 mmol), dodecanethiol **2** (0.6 mmol), $Cu(OAc)_2 \cdot H_2O$ (20 mol %), CuO (2.0 equiv), toluene (2 mL), under air, 120 °C, 8h. [b] Isolated yields.

thioethers could be efficiently obtained from this method. Aliphatic thiols as reaction partners were used for the first time in the direct thiolationof azoles. This approach is simple, general, and practical which complemented the classic methods for the rapid construction of C–S bonds.

Experimental section

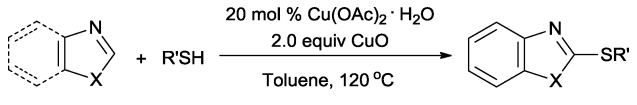
General remarks

Column chromatography was carried out on silica gel. Unless noted ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$, ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on an FT-IR spectrometer and only major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and were uncorrected. All new compounds were further characterized by HRMS (high resolution mass spectra); copies of their ^{1}H NMR and ^{13}C NMR spectra are provided. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene was dried and distilled from sodium/benzophenone.

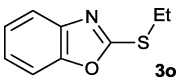
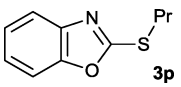
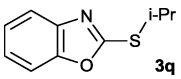
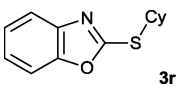
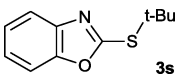
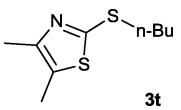
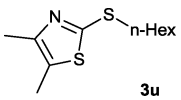
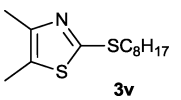
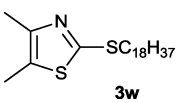
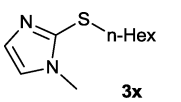
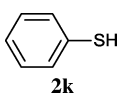
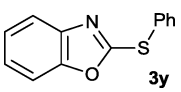
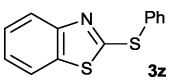
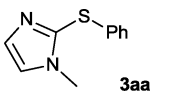
General procedure for the preparation of 3

Under air atmosphere, a reaction vessel was charged with heterocycle **1** (0.4 mmol), RSH **2** (0.6 mmol), $Cu(OAc)_2 \cdot H_2O$ (16 mg, 20 mol%), CuO (64 mg, 0.8 mmol), and PhMe (2 mL). The mixture was stirred at 120 °C and monitored by TLC. After the completion of the reaction, the residue was purified directly by short flash column chromatography on silica gel with hexane/ethyl acetate as an eluent to give the desired corresponding product.

Table 3 Reactions of heterocycles with various thiols[a]



1 2 3

Entry	1	Thiol 2	Product	Yield[b] (%)
1	**1a**	 **2b**	 **3o**	80
2	**1a**	 **2c**	 **3p**	78
3	**1a**	 **2d**	 **3q**	63
4[c]	**1a**	 **2e**	 **3r**	69
5[d]	**1a**	 **2f**	 **3s**	4
6	**1j**	$CH_3(CH_2)_3SH$ **2g**	 **3t**	82
7	**1j**	$CH_3(CH_2)_5SH$ **2h**	 **3u**	81
8	**1j**	$CH_3(CH_2)_7SH$ **2i**	 **3v**	84
9	**1j**	$CH_3(CH_2)_{17}SH$ **2j**	 **3w**	68
10	**1m**	**2h**	 **3x**	77
11[e]	**1a**	 **2k**	 **3y**	33
12[e]	**1g**	**2k**	 **3z**	41
13[e]	**1n**	**2k**	 **3aa**	55

[a] **1** (0.4 mmol), thiol **2** (0.6 mmol), $Cu(OAc)_2 \cdot H_2O$ (20 mol%), CuO (2.0 equiv.), toluene (2 mL), under air, 120 °C, 8 h. [b] Isolated yields. [c] **2e** (0.72 mmol), $Cu(OAc)_2 \cdot H_2O$ (40 mol%) were used. [d] 24 h. [e] **2k** (0.72 mmol), 10 h.

2-(Dodecylthio)benzo[*d*]oxazole (3a). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); white solid, mp: 23.0–24.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.25–1.31 (m, 16H), 1.43–1.50 (m, 2H), 1.78–1.86 (m, 2H), 3.30 (t, J = 7.2 Hz, 2H), 7.20–7.28 (m, 2H), 7.42 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 151.7, 142.0, 124.1, 123.7, 118.3, 109.7, 32.2, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.6, 22.7, 14.1; IR (thin film, cm^{-1}) 2921, 2849, 1503, 1468, 1130, 744; HRMS (ESI) m/z: calcd for $C_{19}H_{29}NOS$ $[M + H]^+$: 320.2043, found: 320.2047.

2-(Dodecylthio)-5-methylbenzo[*d*]oxazole (3b). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); white solid, mp: 29.2–31.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26–1.31 (m, 16H), 1.43–1.50 (m, 2H), 1.77–1.85 (m, 2H), 2.43 (s, 3H), 3.29 (t, J = 7.2 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 150.0, 142.2, 133.9, 124.6, 118.4, 109.1, 32.2, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.6, 22.7, 21.4, 14.1; IR (thin film, cm^{-1}) 2919, 2850, 1637, 1497, 1152, 805; HRMS (ESI) m/z: calcd for $C_{20}H_{31}NOS$ $[M + H]^+$: 334.2199, found: 334.2191.

2-(Dodecylthio)-5-methoxybenzo[*d*]oxazole (3c). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); white solid, mp: 24.8–26.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26–1.31 (m, 16H), 1.43–1.50 (m, 2H), 1.78–1.85 (m, 2H), 3.29 (t, J = 7.2 Hz, 2H), 3.83 (s, 3H), 6.81 (dd, J = 8.8, 2.4 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 157.1, 146.4, 142.8, 111.6, 109.8, 102.0, 55.9, 32.3, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.6, 22.7, 14.1; IR (thin film, cm^{-1}) 2916, 1636, 1476, 1142, 826; HRMS (ESI) m/z: calcd for $C_{20}H_{31}NO_2S$ $[M + H]^+$: 350.2148, found: 350.2143.

6-Chloro-2-(dodecylthio)benzo[*d*]oxazole (3d). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); white solid, mp: 41.2–42.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26–1.30 (m, 16H), 1.45–1.50 (m, 2H), 1.78–1.85 (m, 2H), 3.29 (t, J = 7.2 Hz, 2H), 7.24 (dd, J = 8.4, 1.6 Hz, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 151.9, 140.8, 129.3, 124.7, 118.6, 110.4, 32.4, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.6, 22.7, 14.1; IR (thin film, cm^{-1}) 2915, 2850, 1504, 1467, 1214, 1140, 817; HRMS (ESI) m/z: calcd for $C_{19}H_{28}ClNOS$ $[M + H]^+$: 354.1653, found: 354.1660.

2-(Dodecylthio)-5-nitrobenzo[*d*]oxazole (3e). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); mp: 58.0–59.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26–1.35 (m, 16H), 1.45–1.52 (m, 2H), 1.82–1.89 (m, 2H), 3.34 (t, J = 7.2 Hz, 2H), 7.52 (d, J = 9.2 Hz, 1H), 8.22 (dd, J = 8.8, 1.6 Hz, 1H), 8.46 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 155.3, 145.2, 142.5, 119.9, 114.4, 109.7, 32.6, 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 29.0, 28.6, 22.7, 14.1; IR (thin film, cm^{-1}) 2915, 2851, 2360, 1639, 1527, 1494, 1342, 1108, 819, 736; HRMS (ESI) m/z: calcd for $C_{19}H_{28}ClNOS$ $[M + H]^+$: 365.1893, found: 365.1896.

2-(Dodecylthio)-5-phenyloxazole (3f). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); white solid, mp: 37.8–39.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz,

3H), 1.25–1.31 (m, 16H), 1.41–1.48 (m, 2H), 1.75–1.82 (m, 2H), 3.20 (t, J = 7.2 Hz, 2H), 7.26–7.31 (m, 2H), 7.37–7.40 (m, 2H), 7.56–7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 152.6, 128.8, 128.1, 127.8, 123.7, 123.0, 32.6, 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 28.6, 22.7, 14.1; IR (thin film, cm^{-1}) 2920, 2849, 1633, 1476, 1165, 1121, 759, 689; HRMS (ESI) m/z: calcd for $C_{21}H_{31}NOS$ [M + H]$^+$: 346.2199, found: 346.2190.

2-(Dodecylthio)benzo[*d*]thiazole (3g). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26–1.30 (m, 16H), 1.43–1.50 (m, 2H), 1.77–1.84 (m, 2H), 3.33 (t, J = 7.2 Hz, 2H), 7.25–7.28 (m, 1H), 7.37–7.41 (m, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 153.4, 135.1, 125.9, 124.0, 121.4, 120.8, 33.6, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 22.7, 14.1; IR (thin film, cm^{-1}) 2924, 2852, 2360, 1461, 1428, 1239, 996, 755; HRMS (ESI) m/z: calcd for $C_{19}H_{29}NS_2$ [M + H]$^+$: 336.1814, found: 336.1809.

2-(Dodecylthio)-6-methylbenzo[*d*]thiazole (3h). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26–1.31 (m, 16H), 1.42–1.49 (m, 2H), 1.76–1.84 (m, 2H), 2.44 (s, 3H), 3.31 (t, J = 7.2 Hz, 2H), 7.20 (dd, J = 8.4, 1.2 Hz, 1H), 7.52 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 151.5, 135.3, 134.1, 127.4, 120.9, 120.7, 33.6, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 22.7, 21.4, 14.1; IR (thin film, cm^{-1}) 2920, 1641, 1446, 994, 813, 728; HRMS (ESI) m/z: calcd for $C_{20}H_{31}NS_2$ [M + H]$^+$: 350.1971, found: 350.1980.

2-(Dodecylthio)thiazole (3i). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26–1.30 (m, 16H), 1.40–1.47 (m, 2H), 1.71–1.79 (m, 2H), 3.20 (t, J = 7.2 Hz, 2H), 7.19 (d, J = 3.6 Hz, 1H), 7.65 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 142.7, 118.5, 34.6, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 22.6, 14.1; IR (thin film, cm^{-1}) 2924, 2853, 2360, 1462, 1388, 1301, 1020, 706; HRMS (ESI) m/z: calcd for $C_{15}H_{27}NS_2$ [M + H]$^+$: 286.1658, found: 286.1656.

2-(Dodecylthio)-4,5-dimethylthiazole (3j). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26–1.32 (m, 16H), 1.38–1.43 (m, 2H), 1.68–1.75 (m, 2H), 2.28 (s, 3H), 2.29 (s, 3H), 3.08 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 148.4, 126.4, 34.9, 31.9, 29.6, 29.5, 29.4, 29.3, 29.0, 28.6, 22.6, 14.6, 14.1, 11.2; IR (thin film, cm^{-1}) 2924, 2853, 1642, 1560, 1460, 1420, 1297, 1110, 1020, 723; HRMS (ESI) m/z: calcd for $C_{17}H_{31}NS_2$ [M + H]$^+$: 314.1971, found: 314.1975.

2-(Dodecylthio)-1-methyl-1*H*-benzo[*d*]imidazole (3k). Silica gel column purification with hexane/ethyl acetate (4/1, v/v); white solid, mp: 32.0–33.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.25–1.31 (m, 16H), 1.43–1.50 (m, 2H), 1.75–1.82 (m, 2H), 3.38 (t, J = 7.2 Hz, 2H), 3.63 (s, 3H), 7.18–7.20 (m, 3H), 7.65–7.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 143.5, 136.7, 121.6, 118.1, 108.2, 32.5, 31.8, 29.8, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 22.6, 14.0; IR (thin film, cm^{-1}) 2922, 2851, 1462, 1441, 1362, 1275, 1230, 911, 731; HRMS (ESI) m/z: calcd for $C_{20}H_{32}N_2S$ [M + H]$^+$: 333.2359, found: 333.2362.

1-Benzyl-2-(dodecylthio)-1*H*-benzo[*d*]imidazole (3l). Silica gel column purification with hexane/ethyl acetate (4/1, v/v); white solid, mp: 47.6–49.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.25–1.30 (m, 16H), 1.40–1.45 (m, 2H), 1.73–1.80 (m, 2H), 3.39 (t, J = 7.2 Hz, 2H), 5.27 (s, 2H), 7.10–7.21 (m, 5H), 7.21–7.31 (m, 3H), 7.70 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 143.7, 136.2, 135.7, 128.8, 127.8, 126.8, 121.8, 118.2, 109.0, 47.4, 32.8, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 22.6, 14.1; IR (thin film, cm^{-1}) 2924, 1642, 1440, 731; HRMS (ESI) m/z: calcd for $C_{26}H_{36}N_2S$ [M + H]$^+$: 409.2672, found: 409.2670.

2-(Dodecylthio)-1-methyl-1*H*-imidazole (3m). Silica gel column purification with hexane/ethyl acetate (4/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.25–1.30 (m, 16H), 1.36–1.41 (m, 2H), 1.61–1.68 (m, 2H), 3.05 (t, J = 7.2 Hz, 2H), 3.61 (s, 3H), 6.91 (s, 1H), 7.05 (s, 1H), 7.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 129.1, 121.9, 34.3, 33.1, 31.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 28.6, 22.6, 14.0; IR (thin film, cm^{-1}) 2924, 2853, 1461, 1279, 1124, 1079, 913, 723; HRMS (ESI) m/z: calcd for $C_{16}H_{30}N_2S$ [M + H]$^+$: 283.2202, found: 283.2198.

2-(Dodecylthio)-5-phenyl-1,3,4-oxadiazole (3n). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); mp: white solid, 32.4–34.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26–1.31 (m, 16H), 1.43–1.50 (m, 2H), 1.80–1.87 (m, 2H), 3.29 (t, J = 7.2 Hz, 2H), 7.46–7.51 (m, 3H), 7.99–8.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 164.5, 131.5, 128.9, 126.6, 123.7, 32.6, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.5, 22.6, 14.1; IR (thin film, cm^{-1}) 2921, 2846, 1637, 1468, 1382, 1186, 1064; HRMS (ESI) m/z: calcd for $C_{20}H_{30}N_2OS$ [M + H]$^+$: 347.2152, found: 347.2147.

2-(Ethylthio)benzo[*d*]oxazol (3o). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (t, J = 7.2 Hz, 3H), 3.32 (q, J = 14.8 Hz, 2H), 7.20–7.29 (m, 2H), 7.42–7.44 (m, 1H), 7.59–7.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 151.7, 142.0, 124.2, 123.7, 118.3, 109.8, 26.6, 14.7; IR (thin film, cm^{-1}) 2930, 2868, 1640, 1451, 1238, 1130, 1096, 924, 743; HRMS (ESI) m/z: calcd for C_9H_9NOS [M + H]$^+$: 180.0478, found: 180.0482.

2-(Propylthio)benzo[*d*]oxazole (3p). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 3H), 1.86 (m, 2H), 3.29 (t, J = 7.2 Hz, 2H), 7.20–7.29 (m, 2H), 7.41–7.43 (m, 1H), 7.59–7.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 151.7, 141.9, 124.1, 123.7, 118.3, 109.7, 34.1, 22.7, 13.2; IR (thin film, cm^{-1}) 2965, 2873, 1640, 1500, 1452, 1238, 1214, 1130, 1095, 805, 742; HRMS (ESI) m/z: calcd for $C_{10}H_{11}NOS$ [M + H]$^+$: 194.0634, found: 194.0639.

2-(Isopropylthio)benzo[*d*]oxazole (3q). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, J = 6.8 Hz, 6H), 4.04 (m, 1H), 7.21–7.29 (m, 2H), 7.43 (d, J = 7.6 Hz, 1H), 7.60–7.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 151.5, 142.0, 124.1, 123.8, 118.4, 109.8, 38.3, 23.3; IR (thin film, cm^{-1}) 2968, 2360, 1648, 1500, 1453, 1237, 1128, 1094, 743; HRMS (ESI) m/z: calcd for $C_{10}H_{11}NOS$ [M + H]$^+$: 194.0634, found: 194.0638.

2-(Cyclohexylthio)benzo[*d*]oxazole (3r). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35–1.39 (m, 1H), 1.44–1.66 (m, 5H), 1.78–1.83 (m, 2H), 2.19–2.23 (m, 2H), 3.86–3.93 (m, 1H), 7.20–7.29 (m, 2H), 7.41–7.43 (m, 1H), 7.60 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 151.6, 142.0, 124.1, 123.7, 118.3, 109.8, 46.0, 33.3, 25.7, 25.5; IR (thin film, cm^{-1}) 3056, 2931, 2854, 1498, 1451, 1238, 1128, 1094, 999, 807, 743; HRMS (ESI) m/z: calcd for $C_{13}H_{15}NOS$ [M + H]$^+$: 234.0947, found: 234.0950.

2-(*tert*-Butylthio)benzo[*d*]oxazole (3s). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 9H), 7.26–7.30 (m, 2H), 7.46–7.48 (m, 1H), 7.64–7.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 151.3, 142.0, 124.3, 124.2, 119.0, 109.9, 49.7, 30.9; IR (thin film, cm^{-1}) 2964, 1500, 1452, 1238, 1120, 1089, 806, 743; HRMS (ESI) m/z: calcd for $C_{11}H_{13}NOS$ [M + H]$^+$: 208.0791, found: 208.0789.

2-(Butylthio)-4,5-dimethylthiazole (3t). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.41–1.50 (m, 2H), 1.67–1.74 (m, 2H), 2.28 (s, 3H), 2.30 (s, 3H), 3.09 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 148.4, 126.4, 34.6, 31.3, 21.8, 14.6, 13.5, 11.2; IR (thin film, cm^{-1}) 2958, 2867, 1560, 1419, 1375, 1297, 1111, 1019; HRMS (ESI) m/z: calcd for $C_9H_{15}NS_2$ [M + H]$^+$: 202.0719, found: 202.0724.

2-(Hexylthio)-4,5-dimethylthiazole (3u). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.27–1.33 (m, 4H), 1.39–1.46 (m, 2H), 1.68–1.75 (m, 2H), 2.28 (s, 3H), 2.29 (s, 3H), 3.09 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 148.3, 126.4, 34.9, 31.2, 29.2, 28.3, 22.4, 14.6, 13.9, 11.2; IR (thin film, cm^{-1}) 2925, 2856, 1639, 1419, 1375, 1296, 1111, 1020, 726; HRMS (ESI) m/z: calcd for $C_{11}H_{19}NS_2$ [M + H]$^+$: 230.1032, found: 230.1038.

4,5-Dimethyl-2-(octylthio)thiazole (3v). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.27–1.33 (m, 8H), 1.38–1.43 (m, 2H), 2.28 (s, 3H), 2.29 (s, 3H), 3.08 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 148.3, 126.4, 34.9, 31.7, 29.2, 29.0, 28.6, 22.6, 14.6, 14.0, 11.2; IR (thin film, cm^{-1}) 2924, 2854, 1560, 1461, 1420, 1374, 1296, 1111, 1019, 730; HRMS (ESI) m/z: calcd for $C_{13}H_{23}NS_2$ [M + H]$^+$: 258.1345, found: 258.1343.

4,5-Dimethyl-2-(octadecylthio)thiazole (3w). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); white solid, mp: 36.0–38.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.25 (brs, 28H), 1.38–1.43 (m, 2H), 1.67–1.75 (m, 2H), 2.28 (s, 3H), 2.29 (s, 3H), 3.08 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 148.4, 126.4, 34.9, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 22.7, 14.6, 14.1, 11.3; IR (thin film, cm^{-1}) 2919, 2581, 1560, 1465, 1419, 1020, 909, 734; HRMS (ESI) m/z: calcd for $C_{23}H_{43}NS_2$ [M + H]$^+$: 398.2910, found: 398.2901.

2-(Hexylthio)-1-methyl-1*H*-imidazole (3x). Silica gel column purification with hexane/ethyl acetate (4/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.8 Hz, 3H), 1.26–1.32 (m, 4H), 1.37–1.44 (m, 2H), 1.61–1.69 (m, 2H), 3.05 (t, J = 7.2 Hz, 2H), 3.61 (s, 3H), 6.91 (s, 1H), 7.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 129.1, 121.9, 34.3, 33.1, 31.2, 29.6, 28.2, 22.4, 13.9; IR (thin film, cm^{-1}) 3106, 2927, 2856, 1459, 1414, 1377, 1279, 1124, 914, 728, 685; HRMS (ESI) m/z: calcd for $C_{23}H_{43}NS_2$ [M + H]$^+$: 199.1263, found: 199.1269.

2-(Phenylthio)benzo[*d*]oxazole (3y). Silica gel column purification with hexane/ethyl acetate (4/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.29 (m, 2H), 7.39–7.41 (m, 1H), 7.43–7.47 (m, 3H), 7.59–7.61 (m, 1H), 7.69–7.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 151.9, 142.0, 134.4, 129.8, 129.6, 127.2, 124.3, 119.1, 110.0; IR (thin film, cm^{-1}) 3060, 2925, 1799, 1500, 1450, 1237, 1127, 1093, 1024, 925, 804, 743; HRMS (ESI) m/z: calcd for $C_{23}H_{43}NS_2$ [M + H]$^+$: 228.0478, found: 228.0481.

2-(Phenylthio)benzo[*d*]thiazole (3z). Silica gel column purification with hexane/ethyl acetate (80/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, J = 7.2 Hz, 1H), 7.40–7.55 (m, 4H), 7.66 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 6.8 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 153.9, 135.3, 130.4, 129.9, 126.1, 124.3, 121.9, 120.7; IR (thin film, cm^{-1}) 3059, 2930, 1580, 1458, 1425, 1309, 1237, 1080, 1004, 753, 690; HRMS (ESI) m/z: calcd for $C_{20}H_{31}NS_2$ [M + H]$^+$: 244.0249, found: 244.0252.

1-Methyl-2-(phenylthio)-1*H*-imidazole (3aa). Silica gel column purification with hexane/ethyl acetate (4/1, v/v); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 7.06 (d, J = 1.2 Hz, 1H), 7.11–7.17 (m, 4H), 7.22–7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 134.8, 130.0, 129.1, 127.8, 126.4, 123.7, 33.7; IR (thin film, cm^{-1}) 3056, 2946, 1582, 1456, 1411, 1280, 1122, 1081, 1024, 915, 743, 693; HRMS (ESI) m/z: calcd for $C_{20}H_{31}NS_2$ [M + H]$^+$: 191.0637, found: 191.0640.

Note added after first publication

This article replaces the version published on 7th June 2011, which contained errors in Table 3.

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