Organic & Biomolecular Chemistry

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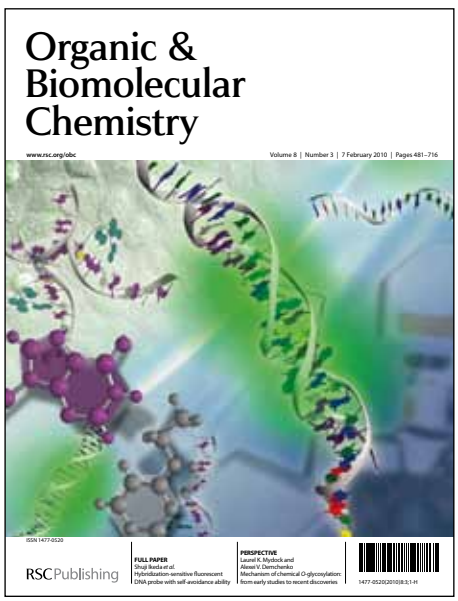

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PAPER

Cu-catalyzed *in situ* generation of thiol using xanthate as thiol surrogate for the one-pot synthesis of benzothiazoles and benzothiophenes†

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A new copper-catalyzed *in situ* generation of aryl thiolates strategy was successfully developed for the one-pot synthesis of substituted benzothiazoles from 2-iodoanilides using xanthate as thiol precursor. A wide range of 2-iodoanilides with both electron-releasing and electron-withdrawing groups produced the corresponding benzothiazoles in good yields. Further, this one-pot protocol was successfully utilized for the synthesis of a potent antitumor agent 2-(3,4-dimethoxyphenyl)-5-fluorobenzo[*d*]thiazole (PMX 610). Finally, copper-catalyzed *in situ* generation of aryl thiolates strategy was successfully applied for the domino synthesis of substituted benzothiophenes from *o*-haloalkynyl benzenes using xanthate as thiol precursor.

Introduction

Benzofused sulfur-containing heterocycles are important class of compounds in pharmaceuticals, biologically active molecules and materials.[1] Particularly, benzothiazole and benzothiophene motifs can be found in numerous biologically important molecules such as antitumor agents,[2] fatty acid amide hydrolase inhibitors[3] and selective estrogen receptor modulators (SERM's) (Fig. 1).[4]

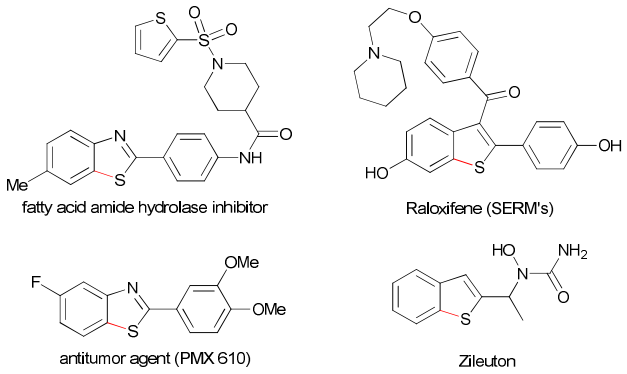

Fig. 1 Biologically active molecules containing benzothiazole and benzothiophene skeleton.

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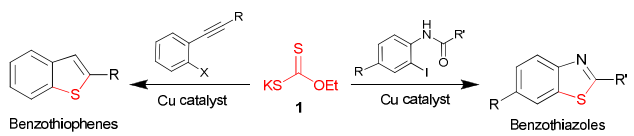
† Electronic supplementary information (ESI) available: (Experimental details, characterization data including ^{1}H NMR spectra, ^{13}C NMR spectra for all compounds)
See DOI: 10.1039/b000000x/

The common methods reported in the literature for the construction of benzothiazole moieties are condensation of 2-aminothiophenols with different electrophiles,[5] C-H functionalized cyclization of thiobenzanilide[6] and transition metal-cnatalyzed intramolecular cyclization of 2-halophenyl benzothioamide.[7] But, these methods are associated with several limitations like usage of readily oxidizable substituted 2-aminothiophenols, formation of regioisomers, limited substrate scope, and high cost of Pd catalysts. In general, thioamides are prepared from the corresponding amides using P_4S_{10} or Lawessons reagent, but it is not feasible for substrates consist of ketone, ester, and amide moieties. The development of Pd or Cu-catalyzed one-pot synthesis of benzothiazoles from 2-haloanilides and a thiol surrogate has overcome these difficulties to a great extent.[8] Towards our ongoing research in developing newer methods for the copper-catalyzed $C_{(aryl)}$-heteroatom bond formation and its application in heterocycles synthesis,[9] recently we have reported a one-pot protocol for the synthesis of aryl thioethers using potassium ethyl xanthogenate (xanthate) **1** as thiol surrogate.[10] To extend the application of our copper-catalyzed *in situ* generation of aryl thiolate strategy, herein, we report a one-pot protocol for the synthesis of benzothiazoles and benzothiophenes using xanthate **1** as a sole thiol precursor (Scheme 1).

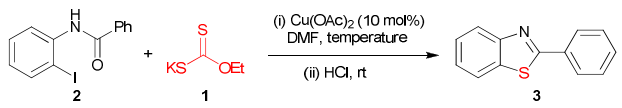


Scheme 1 Cu-catalyzed one-pot synthesis benzothiazoles and benzothiophenes using xanthate as thiol surrogate.

Results and Discussion

We started our studies by reacting *N*-(2-iodophenyl) benzamide **2** with xanthate **1** in the presence of 10 mol% $Cu(OAc)_2$ and 10 mol% of 1,1'-binaphthyl-2,2'-diamine (BINAM) ligand at 105 °C. After 10 hours, *N*-(2-iodophenyl)benzamide **2** was completely consumed, then 0.5 mL of concentrated HCl was added to the reaction mixture and stirred for 8 hours at room temperature to obtain 24% isolated yield of 2-phenylbenzothiazole **3** along with 20% of 2-phenylbenzoxazole (Table 1, entry 1). When the one-pot reaction was carried out without BINAM ligand, in the presence of only $Cu(OAc)_2$, the reaction provided 42% yield of 2-phenylbenzothiazole **3** (entry 2). Similar result was obtained when the reaction was carried out at 80 °C with slightly longer reaction time (entry 3). To increase the efficiency of this one-pot synthesis of benzothiazoles, the amount of xanthate **1** was increased to three equivalents and as a result, a better yield of 62% was obtained (entry 4). Either by changing the copper salt or using external base, the yield for benzothiazole formation decreased (entries 5 and 6). Trace amount of product **3** was observed when the reaction was carried out without $Cu(OAc)_2$ (entry 7).

Table 1 Optimization of reaction conditions for the one-pot synthesis of benzothiazoles



2 1 3

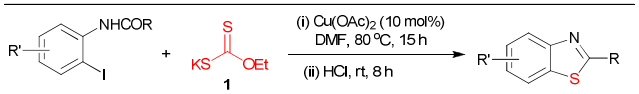
Entry	Equiv. of xanthate	Temperature (°C)	Time (h)	Yield (%)[a]
1	2.0	105	10 + 8	24[b]
2	2.0	105	10 + 8	42
3	2.0	80	20 + 8	40
4	3.0	80	15 + 8	62
5	3.0	80	15 + 8	46[c]
6	1.5	80	15 + 8	32[d]
7	3.0	80	15 + 8	trace[e]

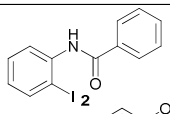
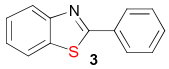
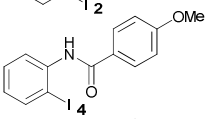
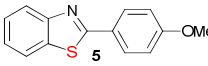
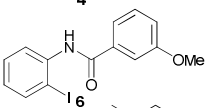
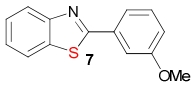
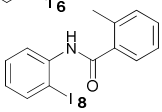
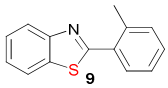
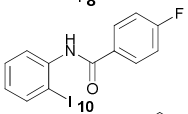
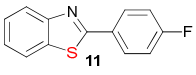
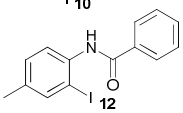
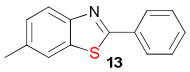
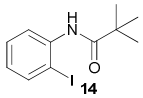
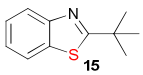
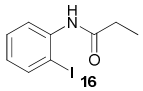
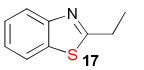
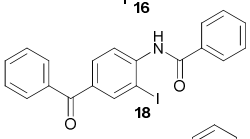
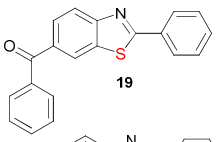
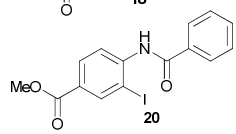
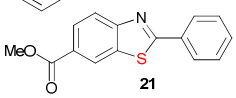
[a] Isolated yield. [b] 10 mol% of BINAM was used. [c] 10 mol% of CuI was used instead of $Cu(OAc)_2$. [d] 2.0 Equivalents of KOH was used after 10 hours. [e] Reaction was carried out without $Cu(OAc)_2$.

Using the above mentioned optimized reaction conditions, we initiated our investigation into the scope of the copper-catalyzed one-pot synthesis of substituted benzothiazoles with a variety of substituted 2-iodoanilides and xanthate **1** as thiol precursor and the results are summarized in Table 2. A wide range of 2-iodoanilides with both electron-releasing (entries 2 and 3) and electron-withdrawing groups (entries 5) produced the corresponding benzothiazoles in good yields. Sterically hindered *ortho*-substituted benzothioamide **8** also provided the corresponding benzothiazole **9** in good yield (entry 4). Interestingly, 2-alkyl-substituted benzothiazoles were also synthesized in good yields (entries 7 and 8). We were pleased to note that under the optimized reaction conditions, 2-iodoanilides containing functional groups such as ketone and ester also provided the corresponding benzothiazoles in good yields (entries 9 and 10).

After completion of a wide range of substituted benzothiazoles synthesis, the one-pot protocol was successfully applied for the synthesis of a potent antitumor agent (PMX 610) 2-(3,4-dimethoxyphenyl)-5-fluorobenzo[*d*]thiazole **25** where 2-arylbenzo[*d*]thiazole formation is the key step (Scheme 2).[2] *N*-(5-Fluoro-2-iodophenyl)-3,4-dimethoxybenzamide **24** was obtained with 87% yield through acylation of 5-fluoro-2-iodoaniline **22** with 3,4-dimethoxybenzoyl chloride **23**. Next, we applied copper-catalyzed one-pot protocol by reacting *N*-(5-fluoro-2-iodophenyl)-3,4-dimethoxybenzamide **24** and xanthate **1** as a thiol precursor. The reaction provided the target molecule antitumor agent 2-(3,4-dimethoxyphenyl)-5-fluorobenzo[*d*] thiazole **25** in 64% isolated yield.

Table 2 Cu-catalyzed one-pot synthesis of benzothiazoles using thiol precursor

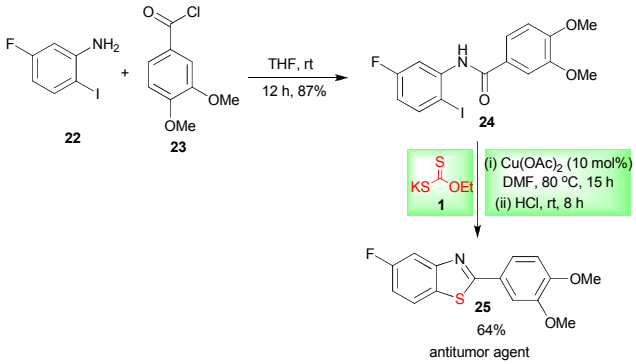


Entry	2-Iodoanilide	Benzothiazole	Yield (%)[a]
1	 2	 3	62
2	 4	 5	75
3	 6	 7	64
4	 8	 9	66
5	 10	 11	56
6	 12	 13	77
7	 14	 15	72
8	 16	 17	64
9	 18	 19	60
10	 20	 21	64

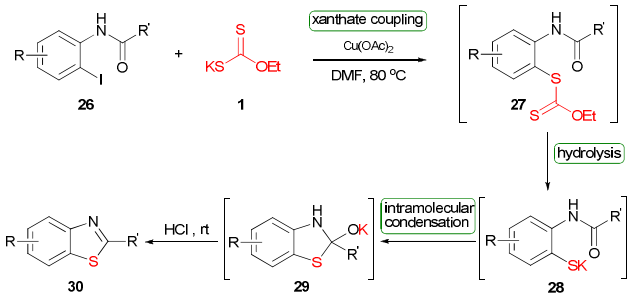
[a] Isolated yield.

The plausible reaction pathway for one-pot synthesis of benzothiazoles is proposed in Scheme 3.[8b] First, there will be a copper-catalyzed Ullmann type $C_{(aryl)}$-S bond formation between 2-iodoanilide **26** with xanthate **1** (xanthate coupling) to give aryl xanthate **27**. Subsequently, this aryl xanthate **27** will be

hydrolyzed by excess xanthate **1** to generate the corresponding aryl thiolate **28** and this *in situ* generated thiolate underwent intramolecular condensation to give the corresponding substituted benzothiazole **30** (Scheme 3). In this one-pot process the *in situ* generation of aryl thiolate **28** was confirmed by trapping with an electrophile (benzyl bromide).[11]



Scheme 2 Synthesis of antitumor agent (PMX 610) using thiol precursor.



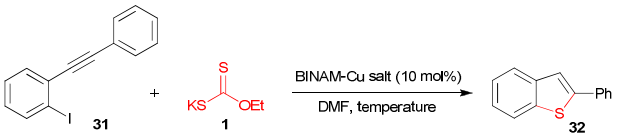
Scheme 3 Plausible reaction pathway for one-pot synthesis of benzothiazoles.

Finally, we extended this *in situ* generation of aryl thiolates methodology for domino synthesis of substituted benzothiophenes from *o*-haloalkynylbenzenes and xanthate **1** as thiol precursor. The common methods reported in the literature for the assembly of benzothiophene moieties are electrophilic cyclization reaction of *o*-alkynylaryl thioether derivatives,[12] intramolecular *S*-arylation of *α*-(*ortho*-haloaryl)thioketones[13] and domino Sonogashira coupling between *o*-bromothiophenol and cuprous acetylide followed by cyclization.[14] But, these methods associated with some limitations like usage of readily oxidizable 2-bromothiophenols, limited substrate scope, moderate yields and high costs of palladium catalysts. The development of transition metal catalyzed one-pot or domino synthesis of benzothiophenes from *o*-haloalkynylbenzenes and a thiol precursor has overcome these difficulties to a great extent.[15]

Initially, the domino reaction was carried out with 1-iodo-2-(phenylethynyl)benzene **31** and xanthate **1** in the presence of 10 mol% of $Cu(OAc)_2$ and 10 mol% of BINAM in DMF at 100 °C and the reaction provided 94% of 2-phenylbenzothiophene **32** (Table 3, entry 1). Similar result was obtained when the reaction was carried out at 80 °C with slightly increased yield (entry 2). The domino reaction provided only 38% of **32** when only $Cu(OAc)_2$ was used as catalyst without ligand BINAM (entry 4).

Using the optimized reaction conditions, a variety of substituted 2-iodoalkynylbenzenes were reacted with xanthate **1** for the domino synthesis of benzothiophenes (Table 4). All types of 2-iodo alkynylbenzenes including electron-releasing, electron-withdrawing and sterically hindered *ortho*-substituted 2-iodoalkynylbenzenes are well tolerated. Heteroatom containing 2-((2-iodophenyl)ethynyl) pyridine **43** also provided 93% isolated yield for the corresponding benzothiophene **44** (entry 7). Less reactive 2-bromoalkynylbenzenes were also used for this domino reaction by slightly increasing the reaction temperature to 100 °C (entries 8-10).

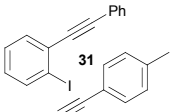
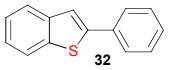
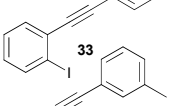
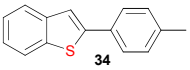
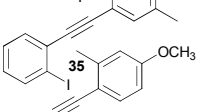
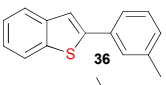
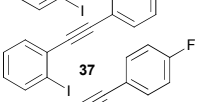
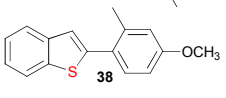
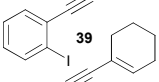
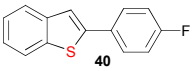
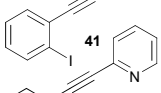
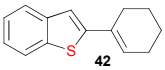
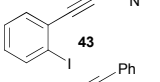
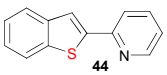
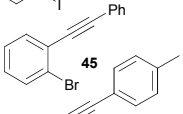
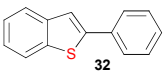
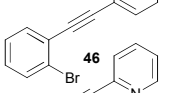
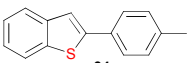
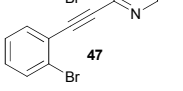
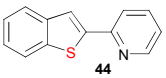
Table 3 Optimization of reaction conditions for the Cu-catalyzed domino synthesis of benzothiophenes



Entry	Cu salt	Temperature (°C)	Time (h)	Yield (%)[a]
1	$Cu(OAc)_2$	100	48	94
2	$Cu(OAc)_2$	80	48	96
3	CuI	80	48	92
4	$Cu(OAc)_2$	80	48	38[b]
5	-	80	72	17[c]

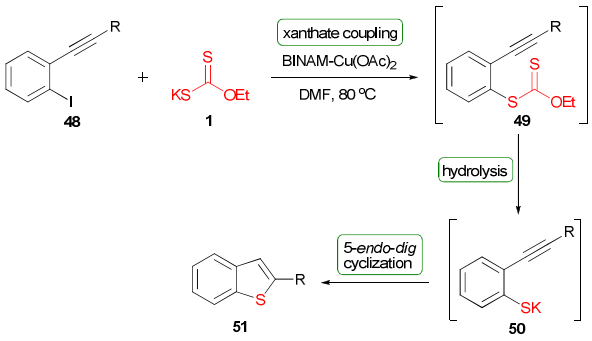
[a] Isolated yield. [b] 10 Mol% of $Cu(OAc)_2$ was used without ligand. [c] Without Cu salt and ligand.

Table 4 Cu-catalyzed domino synthesis of benzothiophenes using thiol precursor

Entry	2-Haloalkyne	Benzothiophene	Yield (%)[a]
1			96
2			96
3			97
4			97
5			99
6			94
7			93
8			68[b]
9			64[b]
10			70[b]

[a] Isolated yield. [b] Reaction was carried at 100 °C for 48 h.

The plausible reaction pathway for domino synthesis of benzothiophenes from *o*-iodoalkynylbenzenes and xanthate **1** is proposed in Scheme 4.[15c] Initially, there will be a copper catalyzed Ullmann type $C_{(aryl)}$-S bond formation between *o*-iodoalkynylbenzene **48** with xanthate **1** (xanthate coupling) to give intermediate **49**. The aryl thiolate **50** is *in situ* generated through the hydrolysis of intermediate **49**, which then underwent intramolecular cyclization to yield the analogous benzothiophene **51** (Scheme 4).



Scheme 4 Plausible reaction pathway for domino synthesis of benzothiophenes.

Conclusion

We have developed a new copper-catalyzed copper-catalyzed *in situ* generation of aryl thiolates strategy for the one-pot synthesis of substituted benzothiazoles from 2-iodoanilides and xanthate as thiol precursor. A wide range of 2-iodoanilides with both electron-releasing and electron-withdrawing groups produced the corresponding benzothiazoles in good yields. Further, this one-pot protocol was successfully utilized for the synthesis of a potent antitumor agent 2-(3,4-dimethoxyphenyl)-5-fluorobenzo[*d*]thiazole (PMX 610). Finally, copper-catalyzed *in situ* generation of aryl thiolates strategy was successfully applied for the domino synthesis of substituted benzothiophenes from *o*-haloalkynyl benzenes and xanthate as a sole thiol precursor.

Experimental Section

General information

1,1'-Binaphthyl-2,2'-diamine (BINAM) ligand was purchased from GERCHEM chemicals, Hyderabad, India. $Cu(OAc)_2 \cdot H_2O$ was purchased from Merck, India and oven dried to obtain anhydrous $Cu(OAc)_2$. Aryl halides, acid chlorides, alkynes and potassium ethyl xanthogenate were purchased from sigma Aldrich Chemical Company. All the solvents used for the reactions were obtained from Rankem, India and dried by Vogel's procedure. Reaction temperatures were controlled by Varivolt temperature modulator, Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized by UV fluorescence quenching. Silica gel (particle size 100-200 mesh) purchased from SRL India was used for chromatography. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument. ^1H NMR spectra were reported relative to Me_4Si (δ 0.0 ppm) or residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.16 ppm). FTIR spectra were recorded on a Nicolet 6700 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were recorded on Q-Tof Micro mass spectrometer.

General procedure for one-pot synthesis of benzothiazoles

A mixture of *N*-(2-iodophenyl)benzamide **2** (161.5 mg, 0.5 mmol), $Cu(OAc)_2$ (9.1 mg, 0.05 mmol) and potassium ethyl xanthogenate **1** (240.4 mg, 1.50 mmol) were taken in an oven-dried reaction tube equipped with a septum. The reaction tube was evacuated and back-filled with nitrogen. *N, N*-Dimethylformamide (3.0 mL) was added to the reaction mixture at room temperature, the reaction tube was sealed with glass stopper and the reaction mixture was heated for 15 hours at 80 °C. Then 0.5 mL conc. HCl was added to the cooled reaction mixture. After 8 hours, 6 mL saturated aq.$NaHCO_3$ was added and the mixture was extracted with ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel using ethyl acetate/hexanes as eluents to give desired product 2-phenylbenzo[*d*]thiazole **3** (65.4 mg, 62%) as white solid.

2-Phenylbenzo[*d*]thiazole (3).[8b] White solid; mp 112-114 °C (lit. 113-114 °C); R_f 0.46 (1:19 ethyl acetate : hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.43 (m, 1H), 7.47-7.54 (m, 4H), 7.91 (d, *J* = 7.6 Hz, 1H), 8.07-8.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.8, 123.4, 125.3, 126.5, 127.7, 129.2, 131.1, 133.7, 135.2, 154.3, 168.2; IR (neat): 3064, 764, 730, 690 cm^{-1}; HRMS (*m/z*): $[M+H]^+$ calcd. for $C_{13}H_{10}NS$: 212.0534; found: 212.0529.

2-(4-Methoxyphenyl)benzo[*d*]thiazole (5).[7a] White solid; mp 121 °C (lit. 120-121 °C); R_f 0.25 (1:19 ethyl acetate : hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 7.00 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 114.5, 121.6, 123.0, 124.9, 126.4, 126.6, 129.3, 135.0, 154.4, 162.1, 168.0; IR (neat): 3063, 2995, 2923, 2837, 832, 758, 623 cm^{-1}; HRMS (*m/z*): $[M+H]^+$ calcd. for $C_{14}H_{12}NOS$: 242.0640; found: 242.0636.

2-(3-Methoxyphenyl)benzo[*d*]thiazole (7).[7b] White solid; mp 82-83 °C (lit. 81-82 °C); R_f 0.65 (1:9 ethyl acetate : hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.04 (dd, *J* = 8.0 & 2.4 Hz, 1H), 7.35-7.43 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 112.1, 117.5, 120.4, 121.7, 123.3, 125.4, 126.5, 130.2, 134.9, 135.1, 154.1, 160.2, 168.1; IR (neat): 3061, 3002, 2932, 2837, 792, 761, 731, 689 cm^{-1}; HRMS (*m/z*): $[M+H]^+$ calcd. for $C_{14}H_{12}NOS$: 242.0640; found: 242.0643.

2-*o*-Tolylbenzo[*d*]thiazole (9).[7b] White solid; mp 52-53 °C (lit. 51-53 °C); R_f 0.58 (1:19 ethyl acetate : hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 2.57 (s, 3H), 7.18-7.35 (m, 4H), 7.38-7.45 (m, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 121.5, 123.5, 125.2, 126.2, 130.1, 130.7, 131.7, 133.2, 135.7, 137.4, 142.6, 153.9, 168.1; IR (neat): 3060, 2964, 2924, 723, 687 cm^{-1}; HRMS (*m/z*): $[M+H]^+$ calcd. for $C_{14}H_{12}NS$: 226.0690; found: 226.0685.

2-(4-Fluorophenyl)benzo[*d*]thiazole (11).[7b] White solid; mp 101-102 °C (lit. 100-102 °C); R_f 0.44 (1:19 ethyl acetate : hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (t, *J* = 8.8 Hz, 2H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.47-7.53 (m, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 8.04-8.12 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.3 (d, *J* = 22.0 Hz), 121.8, 123.3, 125.4, 126.6, 129.7 (d, *J* = 8.7 Hz), 130.1, 135.2, 154.3, 164.6 (d, *J* = 250.4 Hz), 166.9; IR (neat): 3063, 837, 756, 728 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{13}H_9NSF$: 230.0440; found: 230.0438.

6-Methyl-2-phenylbenzo[*d*]thiazole (13).[7b] White solid; mp 149-150 °C (lit. 150-151 °C); R_f 0.28 (1:19 ethyl acetate : hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.45-7.54 (m, 3H), 7.69 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.04-8.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 121.5, 122.9, 127.6, 128.1, 129.1, 130.9, 133.9, 135.4, 135.5, 152.4, 167.1; IR (neat): 3021, 2919, 2852, 815, 766, 690 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{14}H_{12}NS$: 226.0690; found: 226.0698.

2-*tert*-Butylbenzo[*d*]thiazole (15).[16] Pale yellow solid; mp 64-66 °C (lit. 65-67 °C); R_f 0.60 (1:9 ethyl acetate : hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (s, 9H), 7.30-7.37 (m, 1H), 7.41-7.48 (m, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.9, 38.4, 121.6, 122.8, 124.6, 125.8, 135.1, 153.4, 182.0; IR (neat): 2964, 2867, 1511, 1336, 1045, 756, 687 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{11}H_{14}NS$: 192.0847; found: 192.0847.

2-Ethylbenzo[*d*]thiazole (17).[7b] Pale yellow liquid; R_f 0.67 (1:9 ethyl acetate : hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (t, *J* = 7.6 Hz, 3H), 3.16 (q, *J* = 7.6 Hz, 2H), 7.31-7.37 (m, 1H), 7.45 (td, *J* = 8.4 & 1.2 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 27.9, 121.6, 122.6, 124.8, 126.0, 135.1, 153.2, 173.8; IR (neat): 3061, 2974, 2934, 759, 729 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_9H_{10}NS$: 164.0534; found: 164.0538.

Phenyl(2-phenylbenzo[*d*]thiazol-6-yl)methanone (19). White solid; mp 120-122 °C; R_f 0.49 (1:9 ethyl acetate : hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.66 (m, 6H), 7.84 (d, *J* = 7.2 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.08-8.19 (m, 3H), 8.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.9, 124.5, 127.9, 128.4, 128.5, 129.3, 130.1, 131.8, 132.6, 133.3, 134.4, 135.1, 137.9, 156.8, 171.8, 195.9; IR (neat): 3055, 3023, 2922, 2852, 1647, 755, 689 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{20}H_{14}NOS$: 316.0796; found: 316.0801.

Methyl 2-phenylbenzo[*d*]thiazole-6-carboxylate (21).[17] White solid; mp 164-166 °C (lit. 164.5-165.5 °C); R_f 0.53 (1:9 ethyl acetate : hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (s, 3H), 7.50-7.55 (m, 3H), 8.07-8.14 (m, 3H), 8.17 (dd, *J* = 8.4 & 1.6 Hz, 1H), 8.64 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.5, 123.0, 124.0, 127.1, 127.7, 127.9, 129.3, 131.8, 133.4, 135.1, 157.2, 166.8, 171.7; IR (neat): 3062, 3022, 2986, 2945, 2842, 1712, 770, 687 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{15}H_{12}NO_2S$: 270.0589; found: 270.0597.

2-(3,4-Dimethoxyphenyl)-5-fluorobenzo[*d*]thiazole (25).[2] White solid; mp 109-110 °C (lit. 110 °C); R_f 0.32 (1:9 ethyl acetate : hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (s, 3H), 4.02 (s, 3H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.12 (td, *J* = 8.4 & 2.4 Hz, 1H), 7.58 (dd, *J* = 8.4 & 2.0 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.70 (dd, *J* = 9.2 & 2.4 Hz, 1H), 7.78 (dd, *J* = 8.8 & 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.2, 56.3, 109.2 (d, *J* = 23.5 Hz), 109.9, 111.2, 113.6 (d, *J* = 24.8 Hz), 121.3, 122.2 (d, *J* = 9.8 Hz), 126.6, 130.4, 149.5, 151.9, 155.2 (d, *J* = 12.4 Hz), 162.1 (d, *J* = 241.6 Hz), 170.6; IR (neat): 3011, 2961, 2933, 2843, 843, 795 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{15}H_{13}NO_2FS$: 290.0651; found: 290.0654.

Experimental procedure for trapping of aryl thiolate 28

A mixture of *N*-(2-Iodophenyl)pivalamide **14** (151.5 mg, 0.5 mmol), $Cu(OAc)_2$ (9.1 mg, 0.05 mmol) and potassium ethyl xanthogenate **1** (80.1 mg, 0.50 mmol) were taken in an oven-dried reaction tube equipped with a septum. *N, N*-Dimethyl formamide (3.0 mL) was added to the reaction mixture at room temperature, the reaction tube was sealed with glass stopper and the reaction mixture was heated for 10 hours at 80 °C. Then potassium ethyl xanthogenate **1** (160.3 mg, 1.0 mmol) and benzyl bromide (85.5 mg, 0.50 mmol) were added to the reaction mixture and the resulting mixture was further heated to 80 °C for 2.5 hours. The reaction mixture was extracted with ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4 and then the solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel using dichloromethane/ hexanes as eluents to give *N*-(2-(benzylthio)phenyl)pivalamide **28a** (34.2 mg, 23%).

***N*-(2-(benzylthio)phenyl)pivalamide (28a).** Pale yellow oil; R_f 0.23 (1:4 dichloromethane : hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 9H), 3.81 (s, 2H), 6.90-6.97 (m, 3H), 7.12-7.20 (m, 3H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.68 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 40.3, 41.8, 119.9, 122.2, 123.9, 127.6, 128.8, 129.1, 130.4, 136.3, 137.8, 140.6, 176.8; FTIR (neat): 3362, 3062, 3029, 2960, 2926, 2869, 1684, 756, 698, 669 cm^{-1}; HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{22}NOS$: 300.1422; found: 300.1421.

Typical experimental procedure for domino synthesis of benzothiophenes

A mixture of $Cu(OAc)_2$ (9.1 mg, 0.05 mmol), BINAM (14.2 mg, 0.05 mmol) and potassium ethyl xanthogenate **1** (240.4 mg, 1.50 mmol) were taken in an oven dried reaction tube equipped with a septum. The reaction tube was evacuated and back-filled with nitrogen. 1-Iodo-2-(phenylethynyl)benzene **31** (159.1 mg, 0.50 mmol) and *N,N*-dimethylformamide (3.0 mL) were added to the reaction mixture at room temperature. The reaction tube was closed with glass stopper and the reaction mixture was heated for 35 hours at 80 °C. Then, the reaction mixture was allowed to cool to room temperature and extracted with ethyl acetate and saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel using ethyl acetate/hexanes as eluents to give 2-phenylbenzo[*b*]thiophene **32** (101.0 mg, 96%) as white solid.

2-Phenylbenzo[*b*]thiophene (32).[15a] White solid; mp 164-165 °C (lit. 164-166 °C); R_f 0.63 (in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.40 (m, 3H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.56 (s, 1H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.6, 122.4, 123.7, 124.5, 124.6, 126.6, 128.4, 129.1, 134.5, 139.7, 140.8, 144.4; IR (neat): 3052, 3027, 2924, 2855, 752, 731, 690 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{14}H_{11}S$: 211.0581; found: 211.0580.

2-*p*-Tolylbenzo[*b*]thiophene (34).[15a] White solid; mp 167-168 °C (lit. 166.1-168.2 °C); R_f 0.64 (in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.16-7.26 (m, 2H), 7.38 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 118.9, 122.3, 123.5, 124.2, 124.6, 126.5, 129.7, 131.6, 138.4, 139.4, 140.9, 144.5; IR (neat): 3051, 3021, 2913, 2856, 808, 733, 721 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{15}H_{13}S$: 225.0738; found: 225.0742.

2-*m*-Tolylbenzo[*b*]thiophene (36).[15c] White solid; mp 116-118 °C (lit. 117-118 °C); R_f 0.73 (in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.29-7.39 (m, 3H), 7.52-7.56 (m, 3H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 119.4, 122.4, 123.6, 123.7, 124.3, 124.6, 127.3, 128.9, 129.2, 134.3, 138.7, 139.6, 140.8, 144.5; IR (neat): 3056, 3027, 2921, 2854, 832, 786, 747 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{15}H_{13}S$: 225.0738; found: 225.0745.

2-(4-Methoxy-2-methylphenyl)benzo[*b*]thiophene (38). White solid; mp 68-69 °C; R_f 0.37 (in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.85 (s, 3H), 6.79-6.84 (m, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 7.21 (s, 1H), 7.30-7.40 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 55.4, 111.4, 116.3, 122.1, 122.7, 123.4, 124.0, 124.4, 126.8, 131.9, 138.1, 140.1, 140.4, 143.6, 159.7; IR (neat): 3052, 3001, 2962, 2932, 2835, 811, 744, 727 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{16}H_{15}OS$: 255.0844; found: 255.0836.

2-(4-Fluorophenyl)benzo[*b*]thiophene (40).[18] White solid; mp 162 °C (lit. 162-164 °C); R_f 0.69 (in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09-7.16 (m, 2H), 7.30-7.40 (m, 2H), 7.47 (s, 1H), 7.65-7.71 (m, 2H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.1 (d, *J* = 21.8 Hz), 119.6, 122.4, 123.7, 124.5, 124.8, 128.3 (d, *J* = 8.0 Hz), 130.7, 139.6, 140.8, 143.2, 162.9 (d, *J* = 246.8 Hz); IR (neat): 3061, 3033, 821, 745, 727 cm^{-1}.

2-Cyclohexenylbenzo[*b*]thiophene (42).[15b] White solid; mp 85-86 °C (lit. 84-86 °C); R_f 0.72 (in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57-1.64 (m, 2H), 1.69-1.76 (m, 2H), 2.13-2.20 (m, 2H), 2.39-2.45 (m, 2H), 6.23 (t, *J* = 4.0 Hz, 1H), 7.03 (s, 1H), 7.14-7.23 (m, 2H), 7.56-7.60 (m, 1H), 7.65 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 22.8, 25.9, 27.1, 117.9, 122.1, 123.3, 124.2, 124.3, 127.2, 131.7, 138.4, 140.6, 146.9; IR (neat): 3050, 3022, 2927, 2855, 2826, 1632, 817, 740, 722 cm^{-1}; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{14}H_{15}S$: 215.0894; found: 215.0903.

2-(Benzo[*b*]thiophen-2-yl)pyridine (44).[19] White solid; mp 125-126 °C (lit. 126 °C); R_f 0.55 (1:9 ethyl acetate : hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.23 (m, 1H), 7.32-7.39 (m, 2H), 7.73 (td, *J* = 8.0 & 2.0 Hz, 1H), 7.78-7.82 (m, 2H), 7.83 (s, 1H), 7.85-7.90 (m, 1H), 8.62-8.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.7, 121.2, 122.7, 124.2, 124.6, 125.2, 136.7, 140.6, 140.8, 144.9, 149.9, 152.7; IR (neat): 3045, 2991, 782, 752, 738 cm^{-1}.

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Graphical Abstract

Cu-catalyzed *in situ* Generation of Thiol Using Xanthate as Thiol Surrogate for the One-pot Synthesis of Benzothiazoles and Benzothiophenes

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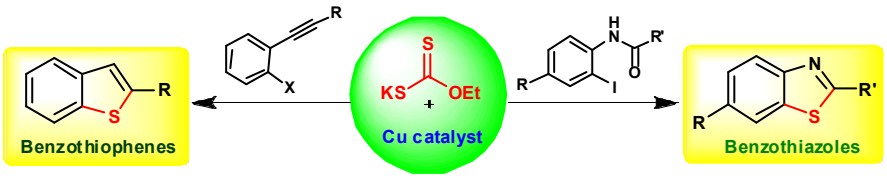

A new copper-catalyzed *in situ* generation of aryl thiolates strategy was successfully developed for the one-pot synthesis of substituted benzothiazoles from 2-iodoanilides using xanthate as thiol precursor. A wide range of 2-iodoanilides with both electron-releasing and electron-withdrawing groups produced the corresponding benzothiazoles in good yields. Further, this one-pot protocol was successfully utilized for the synthesis of a potent antitumor agent 2-(3,4-dimethoxyphenyl)-5-fluorobenzo[*d*]thiazole (PMX 610). Finally, copper-catalyzed *in situ* generation of aryl thiolates strategy was successfully applied for the domino synthesis of substituted benzothiophenes from *o*-haloalkynyl benzenes using xanthate as thiol precursor.