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One-Pot Synthesis of Functionalized Benzo[*b*]thiophenes and Their Hetero- Fused Analogs via Intramolecular Copper Catalyzed S-Arylation of In Situ Generated Enethiolates

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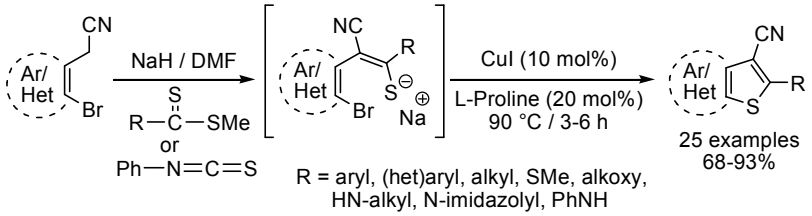


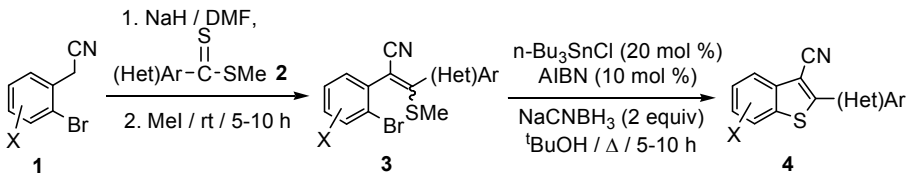
ABSTRACT: An efficient one-pot synthesis of highly functionalized multisubstituted benzo[*b*]thiophenes and their hetero- fused analogs such as thieno[2,3-*b*]thiophenes, indolo[2,3-*b*]thiophenes and pyrazolo[3,2-*c*]thiophenes has been reported. The overall strategy involves sequential base mediated condensation 2-bromo-het(aryl)acetonitrile precursors with (het)aryl/alkyl dithioesters or other thiocarbonyl species such as dimethyl trithiocarbonate, *S*-methyl xanthates, methyl *N*-imidazolyl dithioate, *N*-alkyl dithiocarbamate and phenyl isothiocyanate, followed by intramolecular copper catalyzed arylthiolation of in situ generated enethiolates, furnishing a broad range of 2-functionalized 3-cyano benzo[*b*]- and /hetero- fused thiophenes in high yields.

Benzo[*b*]thiophene and its derivatives represent an important heterocyclic core, because of their frequent occurrence in nature and wide range of biological activity displayed by these

class of compounds.[1] Several marketed drugs contain the benzothiophene core, such as zileuton,[1,2] a potent and selective inhibitor of 5-lipoxygenase, whereas raloxifene and arzoxifene are selective estrogen receptor modulators (SERM).[1,3-4] Also, benzo[*b*]thiophene and its condensed analogs are important structural component in development of optoelectronic materials, including organic photovoltaics and field effect transistors.[1b,5] Therefore research directed towards concise new synthesis of multisubstituted benzo[*b*]thiophenes has been actively pursued in recent years,[1,6] and many efficient methods have been developed.

Among recent syntheses, the most common approach for benzo[*b*]thiophenes involves intramolecular 5-*endo*-*dig* cyclization of *o*-alkynyl arylthioethers or their surrogates, employing electrophilic reagents such as iodine, bromine, NBS, PhSCl or PhSeCl.[5b,5e-f,6a7-9] The methodology has also been extended to transition metal catalyzed cyclization of these analogs, such as Pd,[1b] Cu[10a] or gold catalyzed anulations.[10b-c] 2-Substituted benzothiophenes have also been accessed via tandem intramolecular palladium or copper catalyzed *S*-vinylation and intermolecular cross-coupling reaction of *o*-(gemdibromovinyl)thiophenols.[10e-g] The crucial bond forming event in these reactions is intramolecular attack of nucleophilic sulfur atom on activated C-C multiple bond, leading to the formation of S(1)-C(2) bond of benzothiophene core. These reactions, although selective and efficient, however, require prior synthesis of difficultly accessible prefunctionalized thiophenol precursors.[9] Recently, copper (or Pd) catalyzed double thiolation of *o*-(2-halovinyl)halobenzenes[11a] or 2-bromoalkynylbenzenes[11b] with metal sulfides or its surrogates[11c-d] leading to 2-substituted benzo[*b*]thiophenes has also been reported.[12] These methods involve concomitant formation of S(1)-C(7a) and S(1)-C(2) bonds of benzo[*b*]thiophenes. On the other hand, synthetic approaches to benzothiophenes involving S(1)-C(7a) bond formation via intramolecular C-S coupling-cyclization of α-arylthioenol/enolate

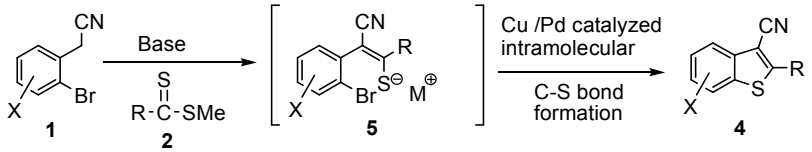
precursors is scarce in the literature. One of the oldest syntheses, which falls under this category, involves iodine[13] or chlorine[14] mediated oxidative cyclization of *β*-aryl-*α*-mercaptoacrylic acids furnishing benzo[*b*]thiophene-2-carboxylic acids in good yields.[15] Recently Willis and co-workers have described synthesis of 2,3-annulated benzo[*b*]thiophenes in moderate to good yields via palladium catalyzed intramolecular cyclization of *o*-(haloaryl)substituted cyclic thioketones.[16a] A palladium catalyzed intramolecular C-H thiolation approach for the direct synthesis of 2,3-diarylbenzo[*b*]thiophenes via Pd chloride oxidative cyclization of 1,2,2-triaryllethenethiols has been recently reported by Inamoto and co-workers.[17] However, the scope of these reactions in terms of functional group/substituent diversity has not been much explored, probably because of the limited accessibility and instability of the requisite thioketone (or thioenol) precursors. During the course of our continued studies directed towards the development of new and efficient methods for five and six membered heterocycles employing novel organosulfur synthons,[18] we have previously reported a novel approach to 2,3-substituted benzo[*b*]thiophenes **4** via intramolecular radical cyclization of 3-(methylthio)-3-(het)aryl/alkyl-1-[2-bromo(het)aryl]acrylonitriles **3** (Scheme 1).[1a,19] These precursors **3** are prepared by base induced condensation of the corresponding 2-bromo(het)aryl acetonitriles **1** with (het)aryl dithioesters **2** followed by in situ *S*-methylation of the resulting enethiolate intermediates (Scheme 1).



Scheme 1. Intramolecular Radical Mediated Synthesis of Benzo[b]thiophenes

During the course of these studies, we conceived of a direct synthesis of benzo[*b*]thiophenes by trapping the corresponding enethiolate intermediates **5** from **1** and **2** and

subjecting them to copper (or palladium) metal catalyzed intramolecular C-S bond formation cyclization in a cascade process (Scheme 2). We have successfully achieved this goal and report in this paper an efficient one pot synthesis of multisubstituted benzo[*b*]thiophenes and their hetero-fused analogs via intramolecular copper catalyzed C-S arylation of in situ generated enethiolate salts **5** involving formation of C(2)-C(3) and S(1)-C(7a) bonds of benzothiophenes in a tandem fashion.

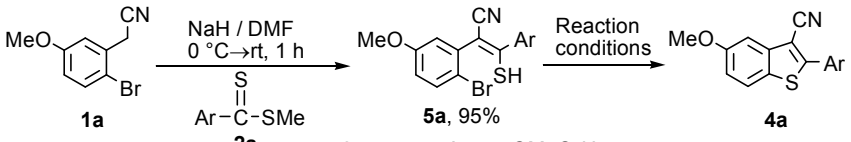


Scheme 2. Proposed Strategy for Synthesis of Benzo[*b*]thiophenes

Initially, 2-bromo-5-methoxyphenylacetonitrile (**1a**) and 4-methoxyphenyldithioester (**2a**) were chosen as model substrates to examine the feasibility and efficiency of the proposed tandem protocol. We first focused on optimization of reaction conditions for a two step process via intramolecular Cu (or Pd) catalyzed cyclization of enethiol intermediate **5a**, which was obtained in 95% yield by condensation of **1a** with **2a** in the presence of base like sodium hydride in DMF as solvent (Table 1). On the other hand, **5a** was obtained in lower yields (20-30%) in the presence of weaker bases like Cs_2CO_3, K_2CO_3 or K_3PO_4 under identical conditions. We first attempted cyclization of **5a** in the absence of any catalyst,[20] which afforded benzo[*b*]thiophene **4a** in 25-30% yields on prolonged heating (Table 1, entries 1-2). Intramolecular thiolation-cross coupling of **5a** to **4a** was next examined under the influence of various copper catalysts, bases and ligands with a view to explore the optimal reaction conditions (Table 1). Thus, our study revealed that benzothiophene **4a** was formed with practically all Cu catalysts in varying yields on heating for prolonged time at 120 ^{o}C (Table 1, entries 3-6), with CuI displaying best results (entry 5). Screening of various bases and ligands (entries 7-14) revealed, that optimal results

were obtained with 10 mol % of CuI, L-proline (20 mol %) as ligand and NaH as base in DMF as solvent, when the reaction was complete within 3 hr at 90 ^{o}C, furnishing the benzothiophene **4a** in 92% yield (entry 12). Decreasing the reaction temperature (entry 15), catalytic loading (entry 16) or changing the CuI/ligand ratio (entries 17-18) required longer time for completion of reaction without much affecting the yield of **4a** (Table 1).

Table 1. Optimization of Reaction Conditions for the Formation of 4a from 5a



entry	Cu catalyst (10 mol %)	base (1 equiv.)	ligand (20 mol %)	temp (°C) /time (h)	% yield
1[a]	-	NaH	-	110 °C /25h	25
2	-	NaH	-	120 °C /28h	30
3	CuCl	-	-	120 °C /18h	73
4	CuBr	-	-	120 °C /18h	71
5	CuI	-	-	120 °C /14h	82
6	Cu_2O	-	-	120 °C /16h	72
7	CuI	K_2CO_3	-	120 °C /11h	83
8	CuI	Cs_2CO_3	-	120 °C /10h	81
9	CuI	K_3PO_4	-	120 °C /12h	79
10	CuI	NaH	-	120 °C /5h	90
11	CuI	KO^{t}Bu	-	120 °C /6h	84
12	CuI	NaH	L-Proline	90 °C /3h	92
13	CuI	NaH	1,10-phen	90 °C /5h	85
14	CuI	NaH	DMEDA	90 °C /5h	85
15	CuI	NaH	L-Proline	50 °C /8h	91
16[b]	CuI	NaH	L-Proline	90 °C /7h	83
17[c]	CuI	NaH	L-Proline	50 °C /10h	87
18[d]	CuI	NaH	L-Proline	50 °C /8h	88

[a] DMSO was used as solvent; [b] with 5 mol % of CuI ; [c] with 1:1 CuI/L-proline ratio; [d] with 1:5 CuI/L-proline ratio

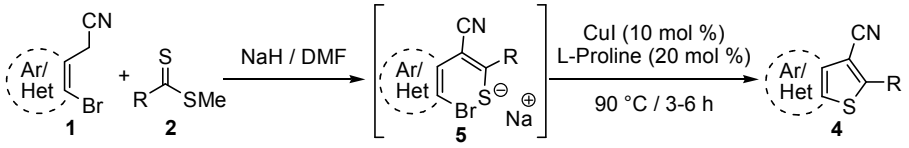
Having accomplished the optimal conditions for intramolecular cyclization of ***5a*** to benzothiophene **4a**, we next aimed to combine synthesis of enethiol **5a**, along with carbon-sulfur

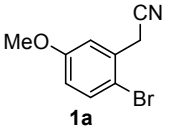
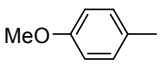
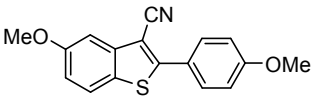
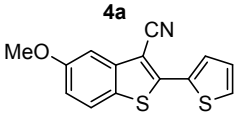
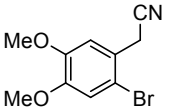
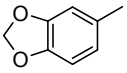
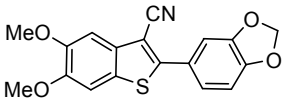
bond forming process in a one pot reaction. Thus in situ generated enethiolate **5a** (from **1a** and dithioester **2a** in the presence of sodium hydride and DMF) was subjected to intramolecular arylthiolation by adding CuI (10 mol %) and L-proline (20 mol %) to the reaction mixture and further heating at 90 °C. Monitoring of the reaction mixture revealed that the reaction was complete within 3 hr, providing benzothiophene **4a** in comparable yield of 90% (Table 2, entry 1).

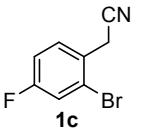
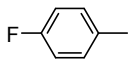
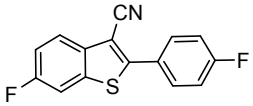
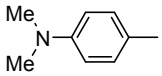
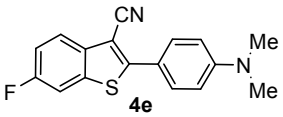
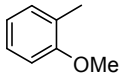
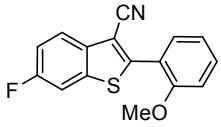
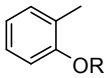
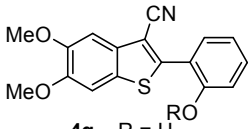
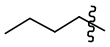
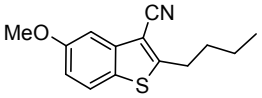
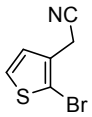
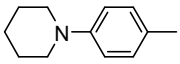
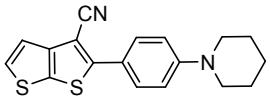
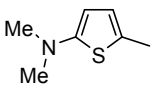
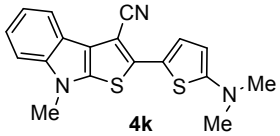
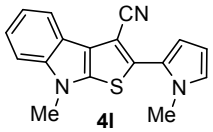
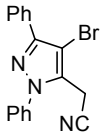
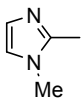
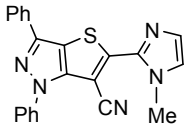
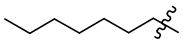
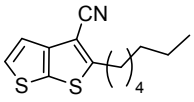
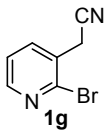
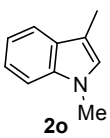
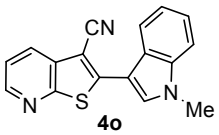
With the optimized reaction conditions in hand, the generality and scope of the present one-pot protocol was explored and the results are summarized in Table 2. Thus aryl group of **1** bearing either the electron donating or withdrawing groups on phenyl ring has little effect on cyclization reaction (entries 1-5). Similarly a range of (het)aryl dithioesters **2** bearing either electron donating/withdrawing/sterically encumbering aryl or hetaryl groups are well tolerated, yielding benzothiophenes **4a-f** in good yields (Table 2, entries 1-6). Attempted cyclization-coupling of **1b** with 2-hydroxyphenyl dithioester **2g** under identical conditions, did not afford the desired 2-(2-hydroxyphenyl)benzothiophene **4g**. However **4g** could be obtained in good yield by two step process via condensation-cyclization of **1b** with 2-(4-methoxybenzyloxy)phenyl dithioester **2h**, furnishing the corresponding 2-[2-(4-methoxybenzyloxy)phenyl]benzothiophene **4h** and its subsequent deprotection with trifluoroacetic acid (Table 2, entries 7-8 and also 17-18). Similarly, using *n*-butyl dithioester **2i**, the corresponding 2-(*n*-butyl)benzothiophene **4i** was obtained in 75% yield (entry 9).The reaction was found to be equally efficient for the synthesis of hetero-fused thiophenes as shown in the entries 10-18 (Table 2). Thus 2,3-substituted thieno[2,3-*b*]thiophenes **4j**, **4n** indolo[2,3-*b*]thiophene **4k-l** and pyrazolo[3,2-*c*]thiophene **4m** could be readily accessed in good yields, by subjecting the corresponding 2-bromo substituted thieno-, indolo-, or pyrazolo- acetonitriles **1d-f** to two step, base mediated condensation - Cu

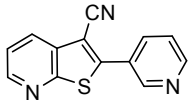
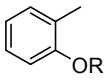
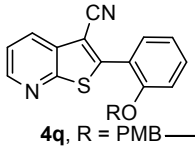
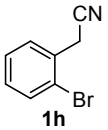
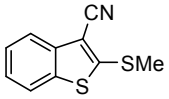
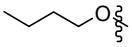
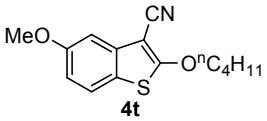
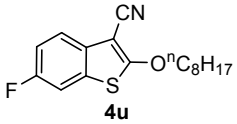
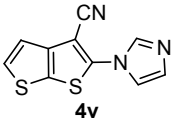
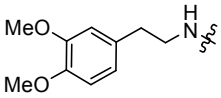
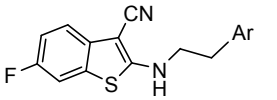
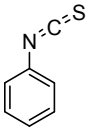
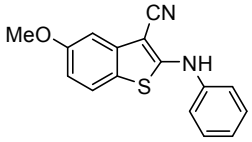
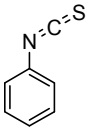
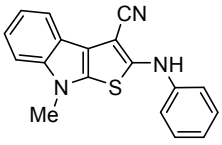
catalyzed intramolecular thiolation process, with various dithioesters **2j-n** under optimized conditions (entries 10-14). The reaction could also be extended for the synthesis of 7-azabenzo[*b*]thiophenes **4o-r** by employing (2-bromopyridyl)-3-acetonitrile **1g** and relevant dithioesters (**2o-p** and **2h**) as coupling partners (Table 2, entries 15-18). Further diversity at 2-position of benzothiophene was introduced by employing a variety of thiocarbonyl substrates such as dimethyl trithiocarbonate **2q**, *O*-alkyl *S*-methyl dithiocarbonate **2r-s**, *N*-imidazolyl dithioate **2t** and *N*-alkyl *S*-methyl dithiocarbamate **2u**, furnishing the corresponding 2-(methylthio)-, 2-(alkoxy)-, 2-(*N*-imidazolyl)- and 2-(Ar)alkylamino- benzo/hetero fused thiophenes **4s-w** respectively in high yields (entries 19-23). Similarly the 2-(anilino)benzo[b]thiophene **4x** or the indolofused analog **4y** could also be synthesized in good yields by using phenyl isothiocyanate as thiocarbonyl component (Table 2, entries 24-25).

Table 2. Syntheses of 2,3-Substituted Benzo[*b*]- and Hetero- Fused Thiophenes 4



entry	**1**	**2**, R	product	yield (%)[a]
1	 **1a**	 **2a**	 **4a**	90
2	**1a**	 **2b**	 **4b**	86
3	 **1b**	 **2c**	 **4c**	73

4	 **1c**	 **2d**	 **4d**	76
5	**1c**	 **2e**	 **4e**	90
6	**1c**	 **2f**	 **4f**	71
7	**1b**	 **2g**, R = H	 **4g**, , R = H	0^{b}; 82^{c}
8	**1b**	**2h**, R = PMB	**4h**, R = PMB	68
9	**1a**	 **2i**	 **4i**	75
10	 **1d**	 **2j**	 **4j**	75
11	 **1e**	 **2k**	 **4k**	80
12	**1e**	 **2l**	 **4l**	84
13	 **1f**	 **2m**	 **4m**	87
14	**1d**	 **2n**	 **4n**	75
15	 **1g**	 **2o**	 **4o**	90

16	**1g**	 **2p**	 **4p**	81
17	**1g**	 **2h**, R = PMB	 **4q**, R = PMB	68
18	-	-	**4r**, R = H (TFA)	79
19	 **1h**	SMe **2q**	 **4s**	88
20	**1a**	 **2r**	 **4t**	93
21	**1c**	n-$C_8H_{17}O$ **2s**	 **4u**	90
22	**1d**	 **2t**	 **4v**	84
23	**1c**	 **2u**	 **4w**, Ar = 3,4-$(OMe)_2C_6H_3$	84
24	**1a**	 **2v**	 **4x**	80
25	**1e**	 **2v**	 **4y**	78

[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol) and NaH (2.0 mmol) in DMF (6 mL), stirred for 1 h; CuI (10 mol%), L-proline (20 mol%) added and heated to 90 °C for 3-5 h; [b]yield with **2g**; [c]yield with **4h**

In summary, we have developed an efficient and practical route to diversely functionalized 2,3-substituted benzo[*b*]thiophenes and hetero fused thiophenes from readily available 2-bromo-(het)arylacetonitriles and (het)aryl/alkyldithioesters and other thiocarbonyl precursors. The overall protocol involves a tandem base mediated condensation of

(het)arylacetonitriles with dithioesters [intermolecular C(2)-C(3) bond formation] followed by a Cu catalyzed intramolecular arylthiolation of the in situ generated thioenolate intermediates [S(1)-C(7a) bond formation] in a one-pot sequence. The new methodology allows direct access to a broad range of benzo/hetero fused thiophenes with a variety of substitution patterns, making it a useful process for structure activity relationship studies. The substrate scope is large and many products have the potential for further synthetic transformations.

Experimental Section

General Information. All reagents were purchased from commercial suppliers and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography using standard TLC Silica gel plates and visualized with UV light. Column chromatography was performed using silica gel (100–200 mesh). Nuclear magnetic resonance spectra were recorded on (400 MHz) FT–NMR spectrometer with $CDCl_3$ (or) DMSO–d_6 as solvent. Chemical shifts were reported in δ ppm using residual solvent protons as internal standard (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO–d_6 in ^{1}H–NMR, δ 77.16 for $CDCl_3$ and δ □39.52 for DMSO–d_6 in ^{13}C–NMR). Coupling constants were reported as *J* values in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), dd (double doublet), dt (doublet of triplet), td (triplet of doublet), ddd (doublet of doublet of doublet), m (multiplet) and br (broad). Infrared spectra of neat samples were recorded in ATR (attenuated total reflectance) mode using FT–IR instrument and HRMS on Q–TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected.

All 2-bromo-(het)aryl acetonitriles **1a-h** were prepared according to the reported procedures.[1a,19] All the known dithioesters **2a-e, 2i-m, 2o-p** and the unknown dithioesters **2f-h**,

2n,[21a] dimethyl trithiocarbonate **2q**,[21b] *O*-alkyl *S*-methyl dithiocarbonates **2r-s**,[21c] methyl N-imidazolyl dithioate **2t,**[21d] [*N*-(3,4-dimethoxphenethyl)] *S*-methyl dithiocarbamate **2u**[21d] and phenyl isothiocyanate **2v**[21e] were also prepared according to the literature procedure. The spectral and analytical data of the new dithioesters **2f-h** and **2n** is given below.

Methyl 2-methoxybenzodithioate (2f). Dark red liquid, (906 mg, 78%): R_f 0.86 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 1592, 1483, 1250, 1040, 882; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.37-7.32 (m, 1H), 6.95 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 6.94-6.92 (m, 1H), 3.82 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 229.6, 154.8, 136.6, 131.3, 129.0, 120.4, 112.0, 56.1, 21.0; HRMS (ESI) m/z calcd for $C_9H_{11}OS_2$ $[M + H]^+$ 199.0251, found 199.0248.

Methyl 2-hydroxybenzodithioate (2g). Red liquid, (944 mg, 71%): R_f 0.75 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 3300-2450, 1607, 1459, 1198, 804; ^1H NMR (400 MHz, $CDCl_3$) δ 12.15 (s, 1H), 8.11 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.42-7.38 (m, 1H), 7.05 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 6.90-6.85 (m, 1H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 226.9, 158.8, 135.1, 127.0, 126.5, 119.9, 119.1, 19.2; HRMS (ESI) m/z calcd for $C_8H_9OS_2$ $[M + H]^+$ 185.0095, found 185.0099.

Methyl 2-(4-methoxybenzyloxy)benzodithioate (2h). Red solid, (908 mg, 86%): mp 60-62 °C; R_f 0.92 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 1611, 1512, 1378, 1243, 1030, 749; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.31-7.27 (m, 3H), 6.96-6.92 (m, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.05 (s, 2H), 3.77 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 229.5, 159.4, 153.9, 137.2, 131.2, 129.0, 128.9, 128.8, 120.7, 114.0, 113.8, 70.7, 55.3, 21.0; HRMS (ESI) m/z calcd for $C_{16}H_{17}O_2S_2$ $[M + H]^+$ 305.0670, found 305.0668.

Methyl octanedithioate (2n). Yellow liquid, (1.2 g, 95%): R_f 0.89 (hexane); IR (neat, cm^{-1}) 2922, 2853, 1457, 1197, 954, 890; ^1H NMR (400 MHz, $CDCl_3$) δ 3.04 (t, J = 7.6 Hz, 2H), 2.61 (s, 3H), 1.83 (quin, J = 7.6 Hz, 2H), 1.37-1.28 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 240.3, 52.1, 31.8, 31.5, 29.1, 28.9, 22.7, 20.1, 14.2; HRMS (ESI) *m/z* calcd for $C_9H_{19}S_2$ $[M + H]^+$ 191.0928, found 191.0919.

Procedure for synthesis of 2-(2-bromo-5-methoxyphenyl)-3-mercapto-3-(4-methoxyphenyl)acrylonitrile (5a). A solution of **1a** (226 mg, 1.0 mmol) in dry DMF (5 mL) was added to a stirred suspension NaH (60% suspension in mineral oil) (80 mg, 2.0 mmol) in DMF (5 mL) at 0 °C, After further stirring for 10 minutes, a solution of 4-methoxyphenyl dithioester (**2a**) was added at 0 °C. The reaction mixture was stirred for 1 h at room temperature (monitored by TLC). It was then diluted with sat. NH_4Cl solution (25 mL), extracted with EtOAc (3 × 25mL) and the combined organic layer was washed with water (3 × 25 mL), brine (2 × 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography using EtOAc/hexane as eluent to give pure **5a**; brown semi-solid (158 mg, 95%): R_f 0.2 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2589, 2221, 1610, 1251, 841; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 9.2 Hz, 1H), 7.53 (d, J = 9.2 Hz, 1H), 6.98-6.95 (m, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 135.4, 134.5, 129.9, 129.0, 119.8, 117.3, 117.0, 116.5, 114.5, 114.2, 113.8, 104.9, 55.7, 55.5; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}BrNO_2S$ $[M + H]^+$ 376.0007 and 377.9986, found 376.0010 and 377.9990.

Procedure for copper catalyzed intramolecular cyclization of enethiol 5a to 5-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene-3-carbonitrile (4a). To a stirred solution of enethiol **5a** (188 mg, 0.5 mmol) in DMF (5 mL), CuI (9 mg, 0.05 mmol), L-proline (12 mg, 1.0 mmol) and

NaH (60% suspension in mineral oil) (18 mg, 0.5 mmol) were added and the reaction mixture was heated at 90 °C with constant stirring for 3 h (monitored by TLC). It was then diluted with sat. NH_4Cl solution (25 mL), extracted with EtOAc (3 × 25mL) and the combined organic layer was washed with water (3 × 25 mL), brine (2 × 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography using EtOAc/hexane as eluent to give pure **4a**; off-white solid (117 mg, 90%): mp 113-115 °C; R_f 0.6 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2214, 1597, 1457, 1257, 1036, 823; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.05 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 3.92 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 158.9, 156.2, 140.8, 129.7, 129.3, 124.3, 123.1, 116.7, 115.8, 114.8, 104.0, 100.6, 55.8, 55.6; HRMS (ESI) m/z calcd for $C_{17}H_{14}NO_2S$ $[M + H]^+$ 296.0745, found 296.0750.

General procedure for two step one-pot synthesis of substituted benzo[*b*]- and hetero-fused thiophenes 4a-y. To a stirring suspension of NaH (60% suspension in mineral oil) (80 mg, 2.0 mmol) in 2 mL of DMF at 0 °C, corresponding 2-bromo(het)arylacetonitrile (**1a-h**) (1.0 mmol) in DMF (2 mL) was added drop wise. After further stirring for 10 minutes, a solution of either respective dithioester (**2a-p**) or thioacarbonyl compound (**2q-v**) (1.0 mmol) in DMF (2 mL) was added to the reaction mixture at 0 °C, followed by further stirring for 1 h at ambient temperature. After complete consumption of starting materials (monitored by TLC), CuI (2 mg, 0.1 mmol) and L-proline (2.5 mg, 0.25 mmol) were added and the reaction mixture was heated at 90 °C with continuous stirring (monitored by TLC). It was then diluted with sat. NH_4Cl solution (25 mL), extracted with EtOAc (3 × 25mL) and the combined organic layer was washed with water (3 × 25 mL), brine (2 × 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The

crude products were purified by silica gel column chromatography using EtOAc/hexane as eluent.

5-Methoxy-2-(thiophen-2-yl)benzo[*b*]thiophene-3-carbonitrile (4b). Obtained from acetonitrile **1a** and dithioester **2b**, off-white solid (103 mg, 86%): mp 150-152 °C; R_f 0.7 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 2212, 1601, 1456, 1211, 1028, 830; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.50 (dd, J = 5.0 Hz, 1.2 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.17 (dd, J = 5.0 Hz, 3.6 Hz, 1H), 7.06 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 148.7, 140.4, 133.9, 132.5, 132.4, 129.0, 128.8, 128.6, 128.5, 123.1, 117.1, 104.2, 55.9; HRMS (ESI) m/z calcd for $C_{14}H_{10}NOS_2$ $[M + H]^+$ 272.0204, found 272.0198.

2-(Benzo[*d*][1,3]dioxol-5-yl)-5,6-dimethoxybenzo[*b*]thiophene-3-carbonitrile (4c). Obtained from acetonitrile **1b** and dithioester **2c**, off-white solid (96 mg, 73%): mp 188-190 °C; R_f 0.8 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2217, 1480, 1257, 1207, 1030, 796; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.29 (s, 1H), 7.22 (s, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.06 (s, 2H), 4.0 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 149.8, 149.6, 149.4, 148.6, 133.1, 129.9, 125.9, 122.7, 115.8, 109.1, 108.3, 103.8, 103.5, 101.9, 101.0, 56.5, 56.4; HRMS (ESI) m/z calcd for $C_{18}H_{13}NNaO_4S$ $[M + Na]^+$ 362.0463, found 362.0449.

6-Fluoro-2-(4-fluorophenyl)benzo[*b*]thiophene-3-carbonitrile (4d). Obtained from acetonitrile **1c** and dithioester **2d**, white solid (96 mg, 76%): mp 140-142 °C; R_f 0.8 (2:8 EtOAc/hexane); IR (Neat, cm^{-1}) 2210, 1604, 1471, 1242, 834; ^1H NMR (400 MHz, DMSO–d_6) δ 7.91 (dd, J = 8.4 Hz, 5.2 Hz, 1H), 7.88-7.83 (m, 2H), 7.55 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.29 (td, J = 8.4 Hz, 2.0 Hz, 1H), 7.25-7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 162.9, 162.7,

160.3, 153.68, 153.65, 138.4, 138.3, 135.6, 130.4, 130.3, 127.61, 127.58, 124.1, 124.0, 116.9, 116.7, 115.7, 115.5, 114.9, 109.1, 108.8, 102.0; HRMS (ESI) *m*/*z* calcd for $C_{15}H_8F_2NS$ $[M + H]^+$ 272.0346, found 272.0351.

2-(4-(Dimethylamino)phenyl)-6-fluorobenzo[*b*]thiophene-3-carbonitrile (4e). Obtained from acetonitrile **1c** and dithioester **2e**, pale yellow solid (125 mg, 90%): mp 167-169 °C; R_f 0.6 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 2212, 1609, 1467, 1202, 813; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83-7.79 (m, 3H), 7.46 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 7.21 (td, J = 9.2 Hz, 2.4 Hz, 1H), 6.76 (d, J = 9.2 Hz, 2H), 3.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 159.8, 156.22, 156.19, 151.8, 137.5, 137.4, 136.2, 129.2, 123.2, 123.1, 118.9, 116.0, 114.9, 114.7, 112.2, 108.8, 108.5, 98.1, 40.2; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{14}FN_2S$ $[M + H]^+$ 297.0862, found 297.0853.

6-Fluoro-2-(2-methoxyphenyl)benzo[*b*]thiophene-3-carbonitrile (4f). Obtained from acetonitrile **1c** and dithioester **2f**, white solid (94 mg, 71%): mp 110-112 °C; R_f 0.7 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 2219, 1464, 1253, 1027, 746; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.8 Hz, 4.8 Hz, 1H), 7.67 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.52 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.49-7.44 (m, 1H), 7.25 (td, J = 8.8 Hz, 2.4 Hz, 1H), 7.09 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 160.0, 156.6, 151.2, 151.1, 139.5, 139.4, 134.9, 132.0, 131.2, 123.8, 123.7, 121.2, 120.2, 115.1, 114.9, 114.8, 111.8, 108.6, 108.4, 104.4, 55.7; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{11}FNOS$ $[M + H]^+$ 284.0545, found 284.0535.

2-(2-(4-Methoxybenzyloxy)phenyl)-5,6-dimethoxybenzo[*b*]thiophene-3-carbonitrile (4h). Obtained from acetonitrile **1b** and dithioester **2h**, off-white solid (115 mg, 68%): mp 165-167 °C; R_f 0.6 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2927, 2212, 1513, 1246, 1003, 757; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.2 Hz, 1.6 Hz, 1H), 7.42-7.38 (m, 1H), 7.34 (d, J = 8.4 Hz,

2H), 7.32 (s, 1H), 7.22 (s, 1H), 7.11-7.07 (m, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.13 (s, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 155.8, 149.44, 149.40, 149.1, 132.2, 131.6, 131.4, 131.3, 129.3, 128.5, 121.4, 121.2, 115.8, 114.1, 113.4, 104.0, 103.5, 103.3, 70.8, 56.41, 56.37, 55.4; HRMS (ESI) m/z calcd for $C_{25}H_{22}NO_4S$ $[M + H]^+$ 432.1270, found 432.1258.

Deprotection of 4h with TFA: **Synthesis of 2-(2-Hydroxyphenyl)-5,6-dimethoxybenzo[*b*]thiophene-3-carbonitrile (4g).** 2-(2-(4-Methoxybenzyloxy)phenyl)-5,6-dimethoxybenzo[*b*]thiophene-3-carbonitrile (**4h**) (100 mg, 0.2 mmol) was dissolved in trifluoroacetic acid (5 mL) and refluxed for 5 h (monitored by TLC). Reaction mixture was poured in ice cold water, extracted with DCM (3 × 25 mL and the combined organic layer was washed with water (3 × 25 mL), brine (2 × 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude products was purified by silica gel column chromatography using EtOAc/hexane as eluent to give pure **4g**; yellow solid (60 mg, 82%): mp 152–154 °C; R_f 0.2 (8:2 EtOAc/hexane); IR (neat, cm^{-1}) 3480-2740, 2219, 1609, 1467, 1202, 813; ^{1}H NMR (400 MHz, DMSO–d_6) δ 9.07 (br s, 1H), 8.25 (s, 1H), 7.75 (d, J = 4.8 Hz, 2H), 7.53-7.49 (m, 1H), 7.36-7.30 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 152.6, 150.5, 149.0, 148.6, 130.6, 130.3, 129.1, 125.0, 124.0, 123.7, 119.4, 117.0, 115.6, 106.5, 104.9, 55.8, 55.5; HRMS (ESI) m/z calcd for $C_{17}H_{14}NO_3S$ $[M + H]^+$ 312.0694, found 312.0690.

2-Butyl-5-methoxybenzo[*b*]thiophene-3-carbonitrile (4i). Obtained from acetonitrile **1a** and dithioester **2i**, yellow liquid (81 mg, 75%): R_f 0.5 (hexane); IR (neat, cm^{-1}) 2927, 2218, 1601, 1459, 1224, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 9.2 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 7.02 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 3.90 (s, 3H), 3.11 (t, J = 7.6 Hz, 2H), 1.78 (quin, J = 7.2 Hz, 2H), 1.45 (sex, J = 7.2 Hz, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ

161.0, 158.8, 139.3, 129.6, 123.3, 116.2, 114.7, 104.3, 103.9, 55.8, 33.3, 30.3, 22.3, 13.8; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{16}NOS$ $[M + H]^+$ 246.0953, found 246.0948.

2-(4-(Piperidin-1-yl)phenyl)thieno[2,3-*b*]thiophene-3-carbonitrile (4j). Obtained from acetonitrile **1d** and dithioester **2j**, brown solid (120 mg, 75%): mp 108-110 °C; R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2932, 2217, 1599, 1235, 764; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 9.2 Hz, 2H), 7.44 (d, J = 5.2 Hz, 1H), 7.32 (d, J = 5.2 Hz, 1H), 6.96 (d, J = 9.2 Hz, 2H), 3.30 (t, J = 5.6 Hz, 4H), 1.72-1.68 (m, 4H), 1.66 (1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 152.7, 146.6, 133.8, 129.3, 128.8, 121.5, 119.2, 116.1, 115.4, 96.8, 49.3, 25.6, 24.5; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{17}N_2S_2$ $[M + H]^+$ 325.0833, found 325.0828.

2-(5-(Dimethylamino)thiophen-2-yl)-8-methyl-8*H*-thieno[2,3-*b*]indole-3-carbonitrile (4k). Obtained from acetonitrile **1e** and dithioester **2k**, orange solid (110 mg, 80%): mp 154-156 °C; R_f 0.3 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2196, 1549, 1492, 1408, 1055, 735; ^1H NMR (400 MHz, DMSO–d_6) δ 7.77 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.33 (td, J = 8.0 Hz, 1.0 Hz, 1H), 7.29 (d, J = 4.4 Hz, 1H), 7.22 (td, J = 8.0 Hz, 1.0 Hz, 1H), 5.98 (d, J = 4.4 Hz, 1H), 3.86 (s, 3H), 2.97 (s, 6H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 160.1, 141.4, 140.8, 138.2, 127.7, 122.8, 120.0, 119.8 ,119.6, 117.5, 116.3, 116.2, 110.4, 102.5, 90.8; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{16}N_3S_2$ $[M + H]^+$ 338.0786, found 338.0782.

8-Methyl-2-(1-methyl-1*H*-pyrrol-2-yl)-8*H*-thieno[2,3-*b*]indole-3-carbonitrile (4l). Obtained from acetonitrile **1e** and dithioester **2l**, off-white solid (98 mg, 84%): mp 191-193 °C; R_f 0.5 (6:4 EtOAc/hexane); IR (neat, cm^{-1}) 2214, 1489, 1302, 1054, 749; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.0 Hz, 1H), 7.40-7.39 (m, 2H), 7.31-7.27 (m, 1H), 6.83 (dd, J = 2.4 Hz, 1.6 Hz, 1H), 6.55 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.26 (dd, J = 3.6 Hz, 2.4 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.9, 135.8, 125.9, 124.0, 123.6, 121.5, 120.8,

120.5, 119.4, 115.8, 113.5, 109.5, 108.9, 100.4, 35.3, 32.5; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{14}N_3S$ $[M + H]^+$ 292.0908, found 292.0897.

5-(1-Methyl-1*H*-imidazol-2-yl)-1,3-diphenyl-1*H*-thieno[3,2-*c*]pyrazole-6-carbonitrile (4m). Obtained from acetonitrile **1f** and dithioester **2m**, off-white solid (98 mg, 87%): mp 259-261 °C; R_f 0.6 (4:6 EtOAc/hexane); IR (Neat, cm^{-1}) 2223, 1518, 1498, 1277, 909, 758; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2H), 7.79-7.77 (m, 2H), 7.59 (t, J = 8.0 Hz, 2H), 7.54-7.41 (m, 4H), 7.29 (s, 1H), 7.15 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 144.2, 143.9, 138.6, 131.1, 131.0, 129.5, 129.2, 129.1, 128.7, 126.2, 124.1, 120.5, 113.2, 94.2, 35.2; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{16}N_5S$ $[M + H]^+$ 382.1126, found 382.1121.

2-Heptylthieno[2,3-*b*]thiophene-3-carbonitrile (4n). Obtained from acetonitrile **1e** and dithioester **2n**, pale yellow liquid (91 mg, 70%): R_f 0.9 (hexane); IR (neat, cm^{-1}) 2205, 1612, 1460, 1201, 840; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 5.2 Hz, 1H), 7.27 (d, J = 5.2 Hz, 1H), 3.07 (t, J = 7.6 Hz, 2H), 1.77 (p, J = 7.6 Hz, 2H), 1.42-1.26 (m, 8H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 161.6, 144.9, 134.5, 129.5, 118.8, 114.6, 101.4, 31.8, 31.6, 30.9, 29.05, 29.01, 22.7, 14.2; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{18}NS_2$ $[M + H]^+$ 264.0881, found 264.0867.

2-(1-Methyl-1*H*-indol-3-yl)thieno[2,3-*b*]pyridine-3-carbonitrile (4o). Obtained from acetonitrile **1g** and dithioester **2o**, brown solid (132 mg, 90%): mp 180-182 °C; R_f 0.3 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2204, 1524, 1378, 1233, 750; ^1H NMR (400 MHz, DMSO–d_6) δ 8.63 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 8.31 (s, 1H), 8.21 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 8.03-8.01 (m, 1H), 7.66-7.64 (m, 1H), 7.61 (dd, J = 8.0 Hz, 4.8 Hz, 1H), 7.38 (td, J = 8.0 Hz, 1.6 Hz, 1H), 7.32 (td, J = 6.8 Hz, 1.2 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 157.0, 149.5,

147.2, 137.0, 131.8, 131.4, 128.8, 124.7, 123.1, 121.6, 119.4, 115.1, 111.2, 105.8, 94.7, 33.2; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{12}N_3S$ $[M + H]^+$ 290.0752, found 290.0750.

2-(Pyridin-3-yl)thieno[2,3-*b*]pyridine-3-carbonitrile (4p). Obtained from acetonitrile **1g** and dithioester **1g**, grey solid (97 mg, 81%): mp 182-184 °C; R_f 0.32 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 2218, 1533, 1385, 1267, 798, 746; ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (br s, 1H), 8.80 (br s, 1H), 8.70 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 8.26 (dd, J = 8.0 Hz, 1.6 Hz, 2H), 7.52 (dd, J = 8.0 Hz, 4.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 158.3, 151.8, 151.0, 149.1, 148.4, 136.0, 131.9, 130.8, 122.1, 113.7, 101.1; HRMS (ESI) *m*/*z* calcd for $C_{13}H_8N_3S$ $[M + H]^+$ 238.0439, found 238.0439.

2-(2-(4-Methoxyphenethyl)phenyl)thieno[2,3-*b*]pyridine-3-carbonitrile (4q). Obtained from acetonitrile **1g** and dithioester **2h**, pale brown solid (128 mg, 68%): mp 112-114 °C; R_f 0.4 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2219, 1514, 1242, 984, 748; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, J = 4.4 Hz, 1.6 Hz, 1H), 8.20 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.76 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.50-7.45 (m, 1H), 7.44 (dd, J = 8.0 Hz, 4.45 Hz, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.15 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 160.1, 160.0, 156.0, 152.2, 148.0, 132.4, 132.1, 131.4, 130.0, 129.5, 128.1, 121.5, 120.8, 114.6, 114.2, 113.4, 102.2, 71.0, 55.4; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{17}N_2O_2S$ $[M + H]^+$ 373.1011, found 373.0985..

2-(2-Hydroxyphenyl)thieno[2,3-*b*]pyridine-3-carbonitrile (4r). Obtained from benzothiophene **4q** by treatment with TFA as for **4g**, brown solid (55 mg, 79%): mp 265-267 °C; R_f 0.2 (9:1 EtOAc/hexane); IR (neat, cm^{-1}) 3490-2850, 2212, 1609, 1459, 1241, 831; ^1H NMR (400 MHz, DMSO–d_6) δ 8.77 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 8.74 (d, J = 3.6 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 7.2 Hz, 1H), 7.69 (dd, J = 8.0 Hz, 4.8 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H),

7.50 (t, J = 7.2 Hz, 1H), ; ^{13}C NMR (100 MHz, DMSO–d_6) δ 159.3, 155.5, 151.3, 150.0, 148.5, 132.5, 131.7, 129.5, 125.2, 125.0, 121.8, 117.2, 116.1, 115.9; HRMS (ESI) m/z calcd for $C_{14}H_9N_2OS$ $[M + H]^+$ 253.0436, found 253.0447.

2-(Methylthio)benzo[*b*]thiophene-3-carbonitrile (4s). Obtained from acetonitrile **1h** and trithiocarbonate **2q**, off-white solid (92 mg, 88%): mp 73-75 °C; R_f 0.7 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2922, 2852, 2210, 1420, 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.46 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.40-7.36 (m, 1H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 154.5, 138.5, 137.8, 126.3, 125.5, 122.0, 121.6, 113.8, 105.2, 19.1; HRMS (ESI) m/z calcd for $C_{10}H_8NS_2$ $[M + H]^+$ 206.0098, found 206.0084.

2-(*n*-Butoxy)-5-methoxybenzo[*b*]thiophene-3-carbonitrile (4t). Obtained from acetonitrile **1a** and xanthate **2r**, white waxy solid (133 mg, 93%): R_f 0.8 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 2921, 2932, 2213, 1539, 1464, 1278, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 8.8 Hz, 1H), 4.31 (t, J = 6.8 Hz, 2H), 3.86 (s, 3H), 1.87 (quin, J = 6.4 Hz, 2H), 1.53 (sex, J = 7.2 Hz, 2H), 1.00 (t, J = 7.6 Hz, 3H)^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 159.1, 136.9, 123.3, 120.7, 114.3, 113.9, 103.8, 86.2, 76.0, 55.7, 31.2, 19.0, 13.8; HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_2S$ $[M + H]^+$ 262.0902, found 262.0913.

6-Fluoro-2-(octyloxy)benzo[*b*]thiophene-3-carbonitrile (4u). Obtained from acetonitrile **1c** and xanthate **2s**, white solid (128 mg, 90%): R_f 0.8 (2:8 EtOAc/hexane); IR (neat, cm^{-1}) 2925, 2215, 1542, 1470, 1238, 818; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 8.8 Hz, 4.8 Hz 1H), 7.35 (dd, J = 4.8 Hz, 2.4 Hz, 1H), 7.18 (td, J = 8.8 Hz, 2.4 Hz, 1H), 4.34 (t, J = 6.8 Hz, 2H), 1.90 (p, J = 6.8 Hz, 2H), 1.49 (p, J = 7.6 Hz, 2H), 1.33-1.29 (m, 8H), 0.89 (t, J = 6.8 Hz, 3H);; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 173.5, 161.5, 159.0, 131.87, 131.85, 129.9, 129.8, 122.3,

122.2, 115.1, 114.9, 113.5, 109.3, 109.0, 85.7, 76.59, 31.8, 29.24, 29.21, 25.7, 22.7, 14.2; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{21}FNOS$ $[M + H]^+$ 306.1328, found 306.1330.

2-(1*H*-Imidazol-1-yl)thieno[2,3-*b*]thiophene-3-carbonitrile (4v). Obtained from acetonitrile **1e** and carbamate **2t**, brown solid (96 mg, 84%): mp 110-112 °C; R_f 0.8 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2218, 1543, 1308, 1079, 749; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.88 (d, J = 5.2 Hz, 1H), 7.75 (br s, 1H), 7.48 (d, J = 5.2 Hz, 1H), 7.24 (br s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 140.9, 140.0, 132.9, 132.3, 122.1, 118.6, 116.7, 113.0, 96.1; HRMS (ESI) *m*/*z* calcd for $C_{10}H_6N_3S_2$ $[M + H]^+$ 232.0003, found 231.9997.

2-(3,4-Dimethoxyphenethylamino)-6-fluorobenzo[*b*]thiophene-3-carbonitrile (4w). Obtained from acetonitrile **1b** and carbamate **2v**, off-white solid (140 mg, 84%): mp 161-163 °C; R_f 0.3 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3309, 2202, 1560, 1468, 1259, 1235, 810; ^1H NMR (400 MHz, DMSO–d_6) δ 8.39 (t, J = 5.6 Hz, 1H), 7.70 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.31 (dd, J = 7.2 Hz, 5.2 Hz, 1H), 7.20 (td, J = 8.8 Hz, 2.4 Hz, 1H), 6.91 (d, J = 1.6 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.80 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.57 (q, J = 6.4 Hz, 2H), 2.89 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 160.5, 158.1, 149.5, 148.4, 134.00, 133.99, 130.0, 129.4, 129.3, 126.8, 120.9, 120.3, 120.2, 115.6, 114.6, 114.3, 112.1, 111.9, 109.0, 109.7, 56.1, 49.2, 35.5; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}FN_2O_2S$ $[M + H]^+$ 357.1073, found 357.1059.

5-Methoxy-2-(phenylamino)benzo[*b*]thiophene-3-carbonitrile (4x). Obtained from acetonitrile **1a** and isothiocyanate **2u**, pale orange solid (100 mg, 80%): mp 181-183 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (Neat, cm^{-1}) 3251, 2198, 1545, 1451, 1293, 758; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.39 (m, 3H), 7.35-7.33 (m, 2H), 7.27 (br s, 1H), 7.22-7.18 (m, 1H), 7.08 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 4.8 Hz, 2.4 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

161.6, 159.1, 140.1, 137.9, 129.9, 125.1, 122.8, 120.9, 120.2, 115.5, 113.1, 103.1, 84.0, 55.8; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{13}N_2OS$ $[M + H]^+$ 281.0749, found 281.0745.

8-Methyl-2-(phenylamino)-8*H*-thieno[2,3-*b*]indole-3-carbonitrile (4y). Obtained from acetonitrile **1e** and isothiocyanate **2u**, brown solid (95 mg, 78%): mp 193-195 °C; R_f 0.4 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3361, 2224, 1600, 1497, 1276, 745; ^1H NMR (400 MHz, DMSO–d_6) δ 9.28 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.34-7.27 (m, 3H), 7.24-7.20 (m, 1H), 7.10-7.08 (m, 2H), 6.31 (t, J = 8.0 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 143.7, 141.1, 135.3, 129.7, 122.9, 122.2, 121.0, 120.3, 119.2, 116.3, 116.1, 115.0, 109.5, 92.8, 32.4; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{14}N_3S$ $[M + H]^+$ 304.0908, found 304.0902.

Supporting information. 30 figures showing scanned copies of ^1H NMR and ^{13}C NMR spectra for compounds **2f-h**, **2n**, **5a** and **4a-y**. This material is available free of charge via the internet at http://pubs.acs.org.

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