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One-pot Synthesis of 2,3-Substituted Benzo[*b*]thiophenes via Cu(I) Catalysed Intramolecular Cyclisation from Dithioesters

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Abstract: Efficient synthesis of benzo[*b*]thiophenes from *o*-halophenyl acetonitrile has been achieved. This novel one-pot procedure involves CuI and pivalic acid catalyzed C-S bond formation using dithioesters followed by a heterocyclization reaction. This efficient protocol has the advantages of one-pot synthesis, short reaction time, good yields (62-78%) and operational simplicity.

Key words*:* S-arylation, benzo[*b*]thiophenes, *o*-halophenyl acetonitrile, heterocyclic compounds and dithioesters.

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Introduction:

Benzo[*b*]thiophene derivatives are important heterocyclic compounds because of their various applications in medicinal chemistry and material science.[1] They represent important heterocyclic cores**,** (Fig 1) which show number of pharmacological properties such as antipsychotic,[2] antidepressive,[3] antithrombolytic,[4] antifungal,[5] antiviral,[6] antiallergic,[7] prostaglandin,[8] dopamine receptor antagonist,[9] and 5-lipoxygenase inhibitor.[10] The 2-arylbenzo[*b*]thiophene derivatives containing these sulfur heterocycles are essential components of clinically important drugs namely, Clopidogrel,[11] Raloxifene [12] and Zileuton.[13] Recently a few 2-arylbenzo[*b*]thiophenes are marketed under the trademark Evista, and these are a class of compounds known as selective estrogen receptor modulators (SERM'S).

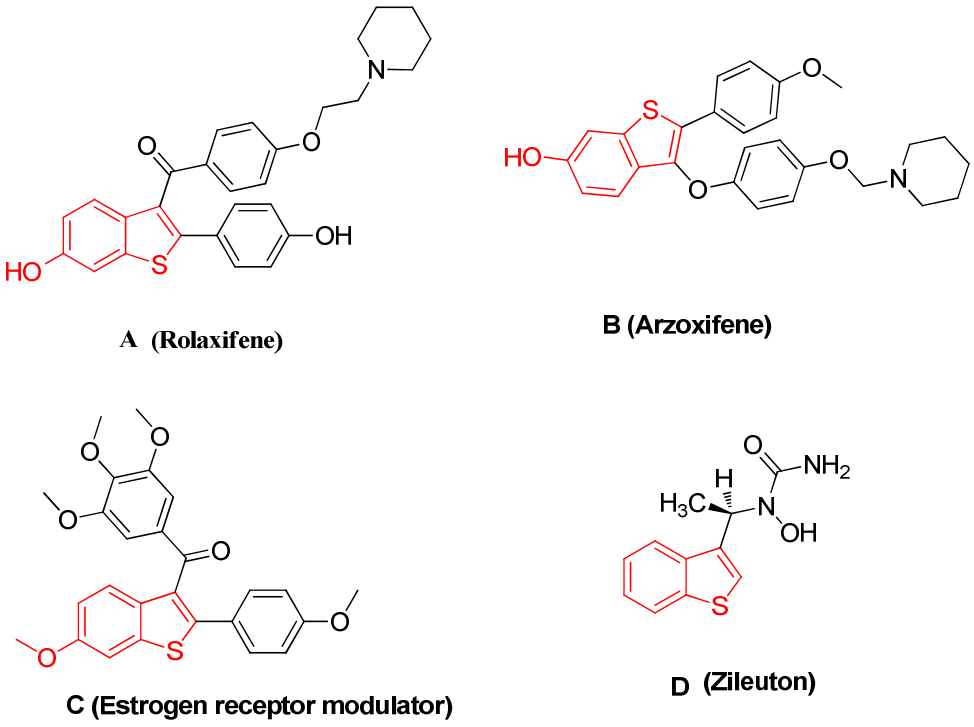
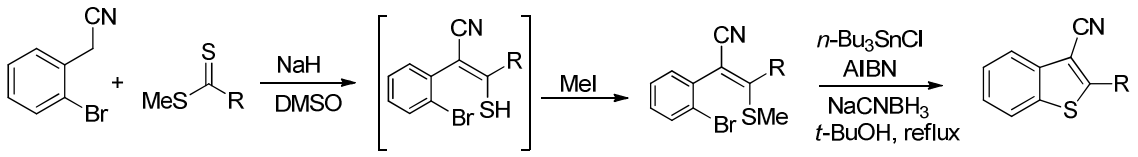


Figure 1 Examples of biologically important benzo[*b*]thiophenes.

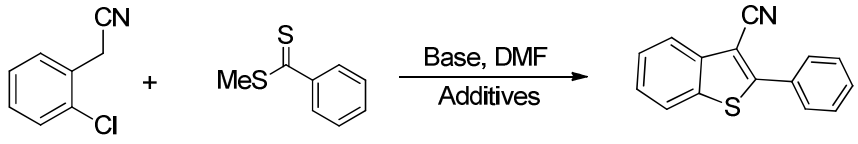
In addition to this, Benzothiophene 3-carbonitrile and corresponding acids have found significant use as building blocks for the synthesis of pharmaceutically important molecules.[14a] Thus, development of general methods for the synthesis of these compounds is valuable in drug discovery. Many methods[14b-i] are reported for the synthesis of benzo[*b*]thiophene and their derivatives such as thiophenol derivatives 2-chlorobenzaldehyde, 2-nitrobenzaldehydes, and alkynyl thiophenols.

The C–S bond formation reactions catalyzed by transition metals[15a] such as palladium,[15b-f] iron,[15g] copper[16] have been reported during the last few years. Nevertheless, the development of Cu-catalyzed methods for C–S bond formation is still attractive owing to the advantages of copper over other metals, like its price and minor toxicity. Sekar and co workers[11] reported the synthesis of benzothiophenes and benzothiozoles in moderate to good yields via copper catalyzed reactions. Recently, Ila *et al*[17] reported synthesis of 2,3-disubstituted benzo[*b*]thiophenes by intramolecular radical cyclization of 2-(*o*-bromoaryl)acrylonitriles derived from *o*-bromoarylacetonitriles using two steps (Scheme 1). Consequently, the development of facile and novel route for the synthesis of these sulfur-based heterocycles is of high interest.



Scheme 1 Synthetic route to 2,3-disubstituted Benzo[*b*]thiophenes

Most of these reported methods involve, hazardous reagents, solvents and this synthetic strategy requires multistep reaction sequence. This encouraged us to consider for a direct reaction in the synthesis of functionalized benzo[*b*]thiophenes. In continuation of our work on synthesis of heterocyclic compounds,[18] herein, we report a novel method to access to benzothiophenes from range of dithioesters via-*S*-arylation



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

Table 1 Optimization of reaction conditions for synthesis of 2-Phenylbenzo[b]thiophene-3-carbonitrile **(3a)**

Entry	Cu catalyst	Pivalic acid	Base (equiv)	Temp ^{o}C	Time in h	yield(%)
1	-	1.5 eq	K_2CO_3 (2)	Reflux	24	-
2	CuI (20 mol%)	1.5 eq	NaH (2)	Reflux	24	54

3	CuI (20 mol%)	1.5 eq	*t*-BuOK (2)	Reflux	24	55
4	CuI (20 mol%)	1.5 eq	Cs_2CO_3 (2)	Reflux	24	20
5	CuI (20 mol%)	1.5 eq	K_3PO_4 (2)	Reflux	4	55
6	CuI (20 mol%)	1.5 eq	K_3PO_4 (2)	100	6	58
7	CuI (20 mol%)	1.5 eq	K_3PO_4 (2)	80	6	62
8	CuI (20 mol%)	1.5 eq	K_3PO_4 (2)	70	24	57
9	CuI (50 mol%)	1.5 eq	K_3PO_4 (2)	80	6	60
10	CuI (10 mol%)	1.5 eq	K_3PO_4 (2)	80	6	57
11	-	1.5 eq	K_3PO_4 (2)	80	6	25
12	CuI (20 mol%)	1.0 eq	K_3PO_4 (2)	80	6	55
13	CuI (20 mol%)	-	K_3PO_4 (2)	80	6	-
14	CuI (20 mol%)	2.0 eq	K_3PO_4 (2)	80	6	57
15	CuI (20 mol%)	1.5 eq	-	80	6	-
16	CuI (20 mol%)	1.5 eq	K_3PO_4 (1.5)	80	6	58
17	CuI (20 mol%)	1.5 eq	K_3PO_4 (2.5)	80	6	60
18	CuBr (20 mol%)	1.5 eq	K_3PO_4 (2)	80	6	52
19	CuOAc (20 mol%)	1.5 eq	K_3PO_4 (2)	80	6	48

[a]General conditions: **1a** (1.0 mmol), **1b** (1.0 mmol) K_3PO_4 (2.0 mmol), in DMF, CuI (20 mol%), pivalic acid (1.5 eq); Yields are isolated yields of chromatographically purified compounds.

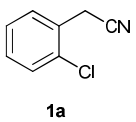
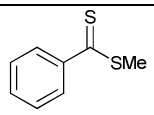
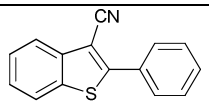
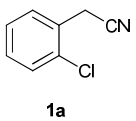
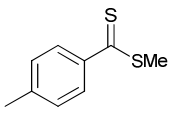
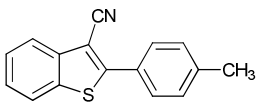
We set out to identify the possible mild conditions under which, the reaction of *o* -chlorophenyl acetonitrile **1a** and phenyl dithioester **2a** would proceed with synthetically useful rate. The reaction requirements including catalysts, bases and additives were screened and the results are listed in Table 1. Initially, the condensation of *o*-chlorophenyl acetonitrile **1a** with phenyl dithioester **2a** was examined in DMF with pivalic acid (1.5 equiv) as an additive, K_2CO_3 (1.5 equiv) as a base, in the absence of CuI, and at reflux, the intermediate product (*E*)-2-(2-bromophenyl)-3-mercapto-3-phenylacetonitrile was isolated in 52% yield. Different inorganic bases were evaluated and results are summarized in (Table 1, entries 1-5). A good result was obtained in presence of K_3PO_4, when the yield of **3a** was increased to 62% (Table 1, entries 5-7). In contrast, no product could be found when organic bases, such as Et_3N and pyridine were used. Remarkably, the reaction was found to proceed efficiently at 80 ^oC. In fact, the highest yield of **3a** (62%) was observed at this point. A reduction in the loading of K_3PO_4 showed negative effect on the yield of **3a** (Table 1, entry 16), whereas increasing to 2.5 equiv of K_3PO_4 did not offer any significant advantage over that of 2 equiv

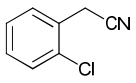
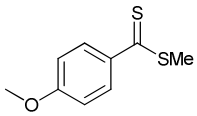
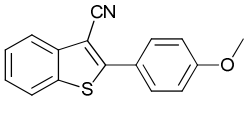
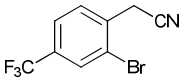
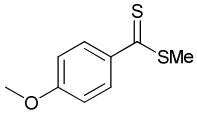
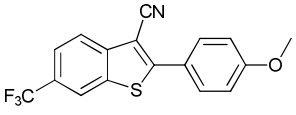
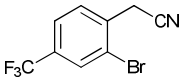
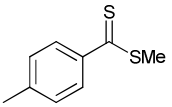
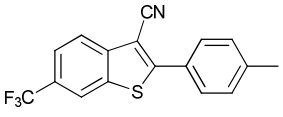
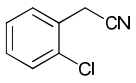
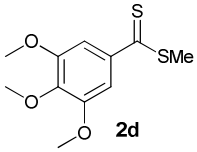
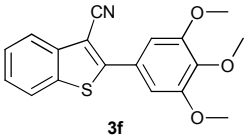
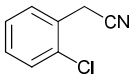
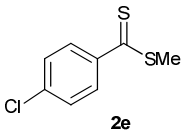
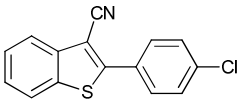
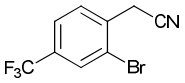
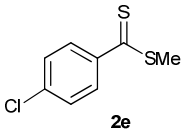
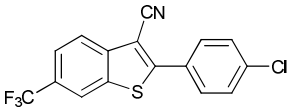
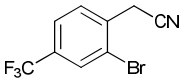
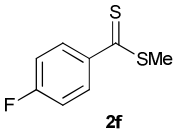
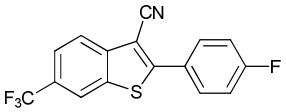
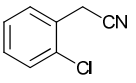
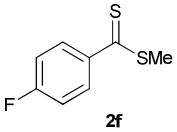
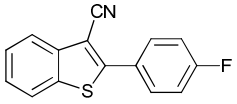
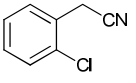
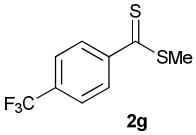
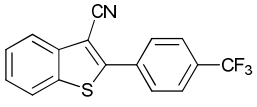
(Table 1, entry 17). Preliminary studies revealed that only DMF, among a variety of other solvents like toluene, DMSO, acetonitrile and THF has proved to give optimal results.

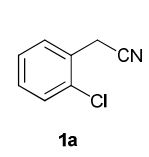
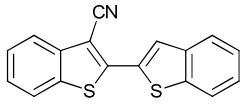
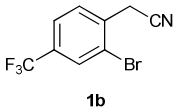
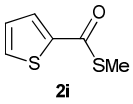
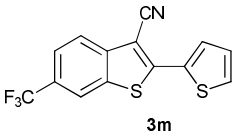
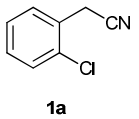
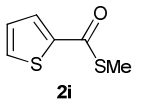
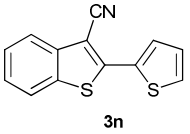
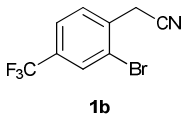
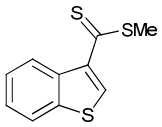
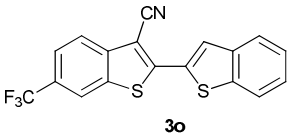
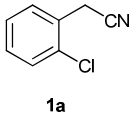
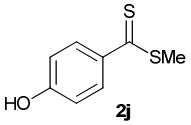
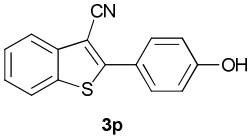
We evaluated the effect of catalyst on the reaction rate and yield, the reaction was found to proceed efficiently in the presence of CuI giving the highest yield of **3a** (62%). An increase in the loading to 50 mol% failed to offer any significant advantages over the 20 mol% catalyst loading (Table 1, entry 9). A reduction in the loading of CuI showed negative effect on the yield of **3a** (Table 1, entry 10), whereas the yield was drastically decreased in the absence of CuI, (Table 1, entry 11). Other copper salts were also tested but CuI remained as the best one (Table 1, entries 18-19). In another set of experiments, effect of additive was tested. A reduction in the loading of pivalic acid had a negative effect on the yield of **3a** (Table 1, entry 12), whereas increasing to 2 equiv did not offer any significant advantages over that of 1.5 equiv catalyst loading (Table1, entry 14). No product was obtained in the absence of pivalic acid (Table1, entry 13).

Copper-catalysed nitrogen free intramolecular C-S bond formation was shown to proceed efficiently with the combination of K_3PO_4 as a base and pivalic acid as an additive. With the optimized reaction conditions established, the substrate scope was examined, and results are summarized in (Table 2). Different dithioesters with electron-donating and electron-withdrawing groups on the benzene ring reacted smoothly with *o*-halophenyl acetonitriles to give the corresponding 2-phenylbenzo[*b*]thiophenes in moderate to good yields at 80 ^{o}C (Table 2). This reaction was not limited to aromatic dithioesters, but heterocyclic dithioester also underwent the reaction equally under mild conditions.

Table 2 Synthesis of 2-aryl/(het) aryl-3-cyanobenzo[*b*] thiophenes using *o*-halophenylacetonitrile and dithioesters**.**

Entry	Substrate	Dithioester	Product	Time in (h)	Yield (%)
1	 **1a**	 **2a**	 **3a**	6.0	62
2	 **1a**	 **2b**	 **3b**	6.0	68

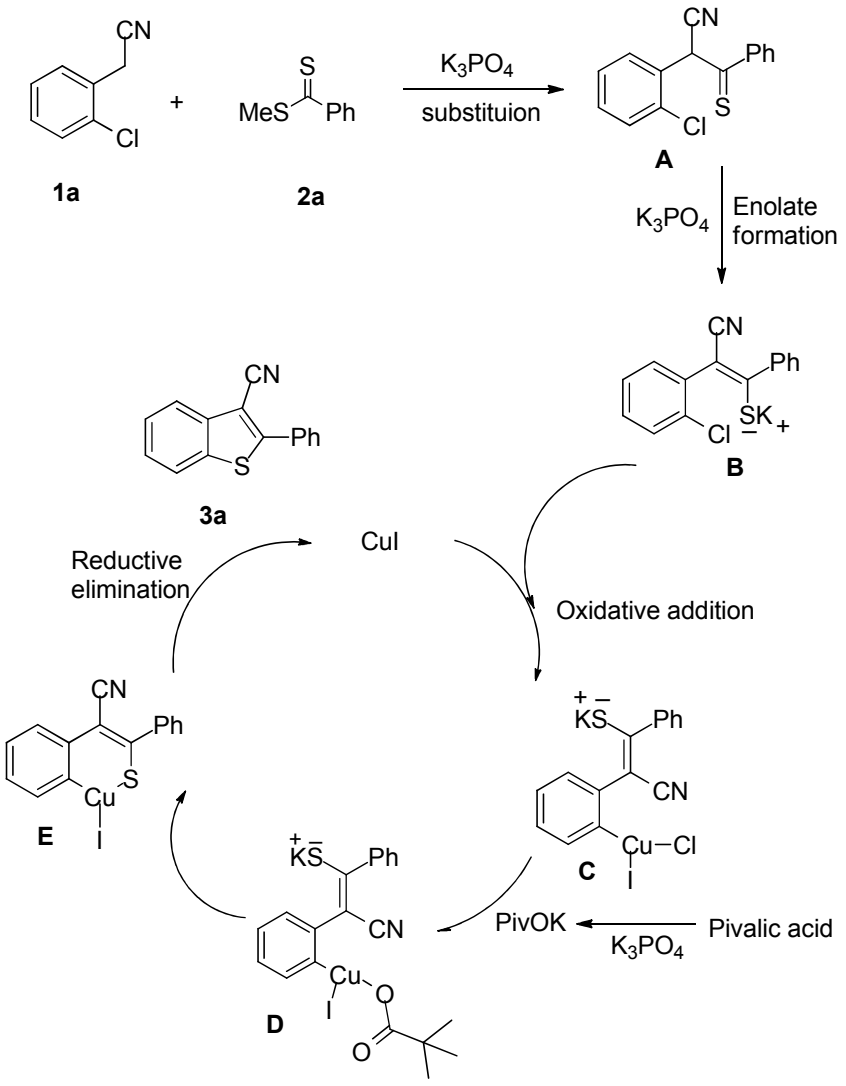
3	 **1a**	 **2c**	 **3c**	6.0	65
4.	 **1b**	 **2c**	 **3d**	5.0	76
5	 **1b**	 **2b**	 **3e**	5.0	71
6.	 **1a**	 **2d**	 **3f**	7.0	65
7	 **1a**	 **2e**	 **3g**	6.0	78
8	 **1b**	 **2e**	 **3h**	6.5	61
9	 **1b**	 **2f**	 **3i**	5.5	75
10	 **1a**	 **2f**	 **3j**	6.0	66
11	 **1a**	 **2g**	 **3k**	6.0	67

12	 1a	 2h	 3l	7.0	72
13	 1b	 2i	 3m	5.5	71
14	 1a	 2i	 3n	5.5	76
15	 1b	 2h	 3o	5.5	69
16	 1a	 2j	 3p	6.5	63

[a]General conditions: **1a** (1.0 mmol), **1b** (1.0 mmol) K_3PO_4 (2.0 mmol), in DMF, CuI (20 mol%), pivalic acid (1.5 eq); [b]Yields are isolated yields of chromatographically purified compounds.

The existence of other halides, such as F and Cl had no significant effect on the reaction, and the desired products were obtained in good yields, (Table 2, entries 7-10), notably, hydroxyl and methoxy were tolerated in the reaction, and the products were obtained in good yields (Table 2, entries 3,4,6 and 16).

A plausible reaction mechanism for the CuI catalyzed domino reaction is presented in Scheme 2. It is assumed that, the reaction starts with abstraction of proton from active methylene compound *o*-chlorophenylacetonitrile followed by the substitution.[19] The second step, is initiated by the reaction of **A** with K_3PO_4 to give the corresponding potassium enolate **B** Later intramolecualr S-arylation between S atom of enolate ion and aromatic carbon carrying the halogen atom is carried out by the oxidative addition of aryl chloride, to copper takes place and **C** is formed as an intermediate. This is followed by exchange of a pivalate for the chloride ligand to give **D**.[20] In the final step **D** undergoes reductive elimination with the formation of benzothiophene **3a** and regeneration of CuI.



Scheme 2: Probable Mechanism for Formation of Benzo[*b*]thiophenes

Conclusion: In summary, we are successful in developing a new efficient method to produce substituted benzothiophene derivatives via copper (I)-catalysed intramolecular C-S bond formation. The overall process is facilitated by the combined action of CuI, K_3PO_4, and pivalic acid. This approach is valuable alternative to widely used thiophenol reactions. This method is complimentary to existing methods for the benzothiophenes. Also, this versatile methodology will be a good alternative for the synthesis of Raloxifene analogues.

Experimental section:

General procedure for the synthesis of 2,3-substituted benzo[*b*] thiophenes: To a solution of 2-(2-chlorophenyl)acetonitrile **(1a)** (1.0 mmol), methyl benzodithioate **(2b)** (1.0 mmol) in

DMF (2 mL), K_3PO_4 (2.0 mmol), pivalic acid (1.5 mmol), cuprous iodide (0.2 mmol) were added. The mixture was stirred at 80 ^oC and progress was monitored by TLC. When the dithioesters could no longer be detected, the reaction mixture was extracted with EtOAc (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.

2-phenylbezo[*b*]thiophene-3-carbonitrile (3a) White solid; yield: 146 mg (62%); MP 172−173 ^oC; R_f= 0.49 (hexane−EtOAc, 9:1). IR (KBr): 2217, 3070, 1608, 1589, 1484, 1318, 1231, 1197, 1064, 943, 878, 744, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.12−7.16 (m, 1H), 7.40−7.53 (m, 5H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ =114.0, 119.4, 122.2, 123.5, 124.2, 124.4, 126.4, 128.2, 128.9, 134.3, 139.5, 140.6, 144.2. MS: m/z= 235 $[M + H]^+$ Anal.Cald for $C_{15}H_9NS$: C, 76.57; H; 3.86; N; 5.95. Found: C, 76.55; H; 3.82; N; 5.91.

2-(p-tolyl)benzo[*b*]thiophene-3-carbonitrile (3b) White solid; yield: 170 mg (68%); MP 166−167 ^oC; R_f= 0.53 (hexane−EtOAc, 9:1); IR (KBr): 2270, 3069, 2925, 1608, 1494, 1343, 1217, 1191, 1065, 941, 859, 746, 687, 617 $cm^{-1;}$ ^1H NMR (400 MHz $CDCl_3$): δ = 7.34 (d, *J* = 10.0 Hz, 2H), 7.42−7.46 (m, 1H), 7.54−7.50 (m, 1H) 7.79−7.85 (m, 3H) 7.97 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.2, 114.0, 118.8, 122.2, 123.3, 124.0, 124.4, 126.3, 129.6, 131.5, 138.2, 139.3, 140.7, 144.4; MS: m/z= 249 $[M + H]^+$; Anal.Cald for $C_{16}H_{11}NS$: C, 77.07; H, 4.45; N, 5.62. Found: C, 77.09; H, 4.40; N, 5.68.

2-(4-methoxyphenyl)benzo[*b*]thiophene-3-carbonitrile (3c) White solid; yield: 173 mg (65%); MP 192−194 ^oC; R_f= 0.46 (hexane−EtOAc, 9:1); IR (KBr): 3095, 2220, 1609, 1528, 1457, 1320, 1208, 1129, 1064, 937, 857, 782, 702, 627 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$): δ = 3.89 (s, 3H), 7.02−7.05 (m, 2H), 7.41−7.45 (m, 1H), 7.49−7.53 (m, 1H), 7.81−7.87 (m, 1H), 7.93 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4, 100.7, 114.7, 115.4, 122.2, 122.3, 124.0, 125.8, 125.9, 129.6, 136.9, 139.9, 155.1, 161.4; MS: m/z= 266 $[M + H]^+$. Anal.Cald for $C_{16}H_{11}NOS$: C, 72.43; H, 4.18; N, 5.28; Found: C, 72.47; H, 4.13; N, 5.24.

2-(4-metoxyphenyl)-6-(trifluromethyl)benzo[*b*]thiophene]-3-carbonitirle (3d) White solid; yield: 254 mg (76%); MP 204−206 ^oC; R_f= 0.55 (hexane−EtOAc, 9:1); IR (KBr): 2215, 1608, 1496, 1318, 1221, 1191, 843, 708, 660, 639 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 3.90 (s, 3H), 7.06 (t *J* =2.5 Hz, 1H), 7.72−7.75 (m, 1H), 7.86−7.89 (m, 2H), 8.03 (d, *J* =

10.5 Hz, 1H), 8.11 (d, *J* = 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6, 119.8, 122.5, 122.8 (q, J_{C-F} = 37.5 Hz, 1C), 122.9, 123.2, 125.4, 127.9, 128.1, 128.6, 129.8, 130.0, 136.6, 141.8, 158.2; MS: m/z= 333 $[M]^+$; Anal.Cald for $C_{17}H_{10}F_3NOS$: C, 61.26; H, 3.02; N, 4.20. Found: C, 61.22; H, 3.08; N, 4.26

2-(*p*-tolyl)-6-((triflurомethyl)benzo[*b*]thiophene]-3-carbonitirle (3e) White solid; yield: 225 mg (71%); MP 183−185 °C; R_f = 0.52 (hexane−EtOAc, 9:1); IR (KBr): 2217, 1593, 1481, 1461, 1322, 1262, 1011, 939, 845, 711, 649 cm^{-1}; ^{1}H NMR (500 MHz $CDCl_3$): δ = 2.32 (s, 3H), 7.27 (d, *J* = 7.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 1H), 8.04 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 114.9, 120.06, 120.09, 123.10, 123.41 (q,J_{C-F} = 38.7Hz,1C), 123.48 123.7, 125.2, 128.31, 128.34, 130.4, 137.1, 141.8, 142.6, 158.6; MS: m/z= 317 $[M]^+$; Anal.Cald for $C_{17}H_{10}F_3NS$: C, 64.34; H, 3.18; N, 4.41. Found: C, 64.37; H, 3.25; N, 4.46.

2-(3,4,5-trimethoxyphenyl)benzo[*b*]thiophene]-3-carbonitirle (3f) White solid; yield: 231 mg (65%); MP 209 −210 °C; R_f= 0.42 (hexane−EtOAc, 9:1); IR (KBr): 3095, 2220, 1609, 1528, 1457, 1320, 1208, 1129, 1064, 937, 857, 782, 702, 627cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.79−3.82 (m, 3H), 3.84−3.92 (m, 6H), 7.04 (s, 2H), 7.33−7.37 (m, 1H), 7. 41−7.45 (m, 1H), 7.72− 7.75 (m, 1H), 7.84−7.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.2, 60.8, 61.0, 101.6, 105.5, 115.3, 122.1, 122.3, 122.59, 125.91, 126.2, 126.7, 137.0, 139.1, 140.1, 153.6, 155.0; MS: m/z= 326 $[M + H]^+$; Anal.Cald for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30; Found: C, 66.47; H, 4.72; N, 4.35

2-(*4*-Chlorophenyl)benzo[*b*]thiophene-3-carbonitrile (3g) White solid; yield: 234 mg (78%); MP 191−193 °C; R_f = 0.59 (hexane−EtOAc, 9:1); IR (KBr): 2217, 1608, 1589, 1484, 1318, 1231, 1197, 1064, 943, 878, 744, 614 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$): δ = 7.46−7.57 (m, 4H), 7.82−7.87 (m, 3H), 7.97−7.99 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 102.5, 114.9, 122.4, 122.7, 126.3, 126.4, 129.5, 129.7, 130.0, 136.7, 137.4, 139.1, 153.5; MS: m/z= 270 $[M + H]^+$; Anal.Cald for $C_{15}H_8ClNS$: C, 66.79; H, 2.99; N, 5.19. Found: C, 66.74; H, 2.93; N, 5.16.

2-(*4*-Chlorophenyl)-6-(triflurомethyl)benzo[*b*]thiophene-3-carbonitrile (3h) White solid; yield: 205 mg (61%); MP 212−214 °C; R_f = 0.58 (hexane−EtOAc, 9:1); IR (KBr): 2919, 2210, 1601, 1525, 1421, 1395, 1229, 1060, 938, 837, 744, 615 cm^{-1}; ^{1}H NMR (400 MHz

$CDCl_3$): δ = 7.52−7.55 (m, 2H), 7.76−7.79 (m, 1H), 7.83 7.87 (m, 2H), 8.09 (d, *J* = 10.5 Hz, 1H), 8.15 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.4, 114.4, 120.1, 122.6, 122.9, 123.6 (q, J_{C-F} = 40 Hz, 1C), 124.0, 128.6, 128.9, 129.4, 137.1,137.6, 141.5, 156.6; MS: m/z= 337 $[M]^+$; Anal.Cald for $C_{16}H_7ClF_3NS$: C, 56.90; H, 2.09; N, 4.15. Found: C, 56.95; H, 2.15; N, 4.18.

2-(*4*-Flurophenyl)-6-(trifluromethyl)benzo[*b*]thiophene-3-carbonitrile (3i) White solid; yield 240 mg (75%); MP 216−218 ^oC; R_f= 0.40 (hexane−EtOAc, 9:1); IR (KBr): 2962, 2215, 1602, 1531, 1460, 1318, 1260, 1162, 1027, 934, 852, 723, 646 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 10.5 Hz, 2H), 7.07 (d, *J* = 10.5 Hz, 1H), 7.81−7.85 (m, 2H), 8.00 (d, *J* = 9.8 Hz, 1H), 8.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.3, 119.8, 122.5, 123.1, 123.7 (q, J_{C-F} = 60 Hz,1C), 124.3, 127.0, 128.7, 129.8, 130.4, 141.4, 156.7, 163.0, 164.5 (d, J_{C-F} =150Hz 1C); MS: m/z = 321 $[M]^+$; Anal.Cald for $C_{16}H_7F_4NS$: C, 59.81; H, 2.20; N; 4.36. Found: C, 59.85; H, 2.25; N; 4.38.

2-(4-flurophenylbezo[*b*]thiophene-3-carbonitrile (3j) White solid; yield: 167 mg (66%); MP 161−163 ^oC; R_f= 0.57 (hexane−EtOAc, 9:1); IR (KBr): 2282, 2215, 1460, 1436, 1318, 1260, 1162, 1027, 934, 852, 723, 646 cm^{-1}; ^{1}H NMR (500 MHz $CDCl_3$): δ = 7.81 (d, *J* = 7.5 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.68−7.65(m, 1H), 7.46 (s, 1H), 7.35-7.31 (m, 2H), 7.13−7.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 115.8, 116.0, 119.4, 122.2, 123.5, 124.3, 128.1, 128.2, 130.56, 140.6, 143.0, 161.7, 162.0 (d, J_{C-F} = 238 Hz 1C); MS: m/z= 254 $[M + H]^+$; Anal.Cald for $C_{15}H_8FNS$: C, 71.13; H, 3.18; N, 5.53.

2-(4-(trifluromethyl)phenyl)benzo[*b*]thiophene-3-carbonitrile (3k) White solid; Yield: 203 mg (67%); MP 216−218 ^oC; R_f= 0.46 (hexane−EtOAc, 9:1); IR (KBr): 2217, 2,231, 3070, 1608, 1589, 1484, 1318, 1176, 1231, 1197, 1064, 943, 878, 744, 614; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.0 Hz, 1H),7.82−7.80 (m 3H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.63 (s, 1H), 7.40−7.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ =114.0, 121.9, 122.9, 123.9, 124.9, (q, J_{C-F} = 103.2 Hz, 1C), 125.1, 125.8, 126.0, 129.8, 130.1, 137.7, 139.8, 140.4, 142.3; MS: m/z= 303 $[M]^+$; Anal.Cald for $C_{16}H_8F_3NS$: C, 63.36; H, 2.66; N, 4.62. Found: C, 63.33; H, 2.63; N, 4.66

2,6-bibenzo[*b*]thiophene]-3-carbonitrile (3l) White solid; yield: 209 mg (72%); MP 153−155 ^oC; R_f= 0.54 (hexane−EtOAc, 9:1); IR (KBr): 3082, 2215, 1531, 1456, 1318, 1256,

1056, 901, 876, 751, 628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.46−7.52 (m, 3H), 7.53−7.60 (m, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.95−7.97 (m, 2H), 8.04-8.15 (m,1H), 8.14−8.16 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 114.7, 122.6, 122.8, 123.0, 125.1, 125.3, 126.2, 126.9, 129.35, 129.3, 136.6, 137.8, 138.2, 138.2, 140.4, 148.2; MS: m/z= 292 $[M + H]^+$; Anal.Cald for $C_{17}H_9NS_2$: C, 70.07; H, 3.11; N, 4.81. Found: C, 70.04; H, 3.18; N, 4.86.

2-(thiophenyl-2-yl)-6-(trifluoromethyl)benzo[*b*]thiophene-3-carbonitrile (3m) White solid; Yield: 219 mg (71%); MP 147−148 ^oC; R_f= 0.57 (hexane−EtOAc, 9:1); IR (KBr): 2217, 1602, 1533, 1531 1497, 1459, 1279, 1119, 1082, 948, 849, 787, 629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20−7.22 (m, 1H), 7.59, (dd, *J* = 7.5, 5.0 Hz, 1H), 7.73−7.75 (m, 1H), 7.84, (dd, *J* = 6.3, 5.0 Hz, 1H), 8.02 (d, *J* = 10.5 Hz, 1H), 8.08 (t, *J* = 0.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.4, 119.6, 122.5, 122.8 (q, J_{C-F} = 36.1 Hz, 1C), 123.1, 123.4, 128.3, 128.6, 129.4, 129.9, 132.8, 136.2, 141.2, 150.6; MS: m/z= 309 $[M]^+$; Anal.Cald for $C_{14}H_6F_3NS_2$: C, 54.36; H, 1.96; N, 4.53.

2-(thiophen-2-yl)benzo[*b*]thiophene-3-carbonitrile (3n) Pale yellow solid; Yield: 206 mg (76%); MP 152-154 ^oC; R_f= 0.50 (hexane−EtOAc, 9:1); IR (KBr): 2217, 1606, 1533, 1497, 1459, 1279, 1119, 1082, 948, 849, 787, 629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.17−7.19 (m, 1H,), 7.45 (t, *J* = 9.5 Hz, 1H), 7.53 (t, *J* = 7.0 Hz, 2H), 7.80 (t, *J* = 10.5 Hz, 2H), 7.92 (d, *J* = 10 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.0, 122.1, 122.4, 126.2, 128.4, 128.6, 128.63, 128.8, 128.9, 133.5, 136.6, 138.8, 147.6; MS: m/z= 242 $[M+H]^+$; Anal.Cald for $C_{13}H_7NS_2$: C, 64.70; H, 2.92; N, 5.80; Found: C, 64.79; H, 2.96; N, 5.88.

6-trifluromethyl)-[2,6-bibenzo[*b*]thiophene]-3-carbonitirle (3o) White solid; yield: 248 mg (69%); MP 159−160 ^oC; R_f = 0.44 (hexane−EtOAc, 9:1); IR (KBr): 2915, 2848, 2214, 1537, 1459, 1363, 1232, 1191, 1057, 898, 754 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ = 7.46−7.54 (m, 2H), 7.79−7.88 (m, 1H), 7.95−7.97 (m, 1H), 8.10−8.14 (m, 3H), 8.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.2, 119.9, 122.1, 122.5 (q, J_{C-F} = 45.5 Hz,1C), 122.6, 123.0, 125.2, 126.3, 128.3, 128.7, 130.23, 130.24, 136.3, 137.4, 140.5, 151.2; MS: m/z= 359 $[M]^+$; Anal.Cald for $C_{18}H_8F_3NS_2$: C, 60.16; H, 2.24; N, 3.90.

2-(4-hydrxoyphenyl)benzo[*b*]thiophene-3-carbonitrile (3p) White solid; Yield: 158 mg (63%); MP 203 ^oC; R_f= 0.49 (hexane−EtOAc, 9:1) IR (KBr): 2217, 3070, 3650, 1608, 1589,

1484, 1318, 1231, 1197, 1064, 943, 878, 744, 614 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ = 6.99−7.50 (m. 2H), 7.50−7.52(m, 1H), 7.54−7.61 (m, 1H), 7.75−7.70 (m, 2H), 7.65−7.67 (m, 1H), 8.11−8.14 (m, 1H), 10.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 104.2, 114.4, 119.6, 120.4, 121.5, 121.6, 126.8, 128.0, 134.7, 135.0, 141.4, 143.6, 160.8, 165.0; MS: m/z= 251 $[M]^+$; Anal.Cald for $C_{15}H_9NOS$: C, 71.69; H, 3.61; N, 5.57. Found: C, 71.65; H, 3.65; N, 5.53.

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