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

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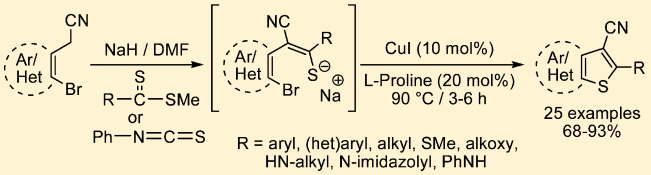
Supporting Information

ABSTRACT: An efficient one-pot synthesis of highly functionalized multisubstituted benzo[*b*]thiophenes and their hetero-fused analogues, 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 of 2-bromohet(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-cyanobenzo[*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 the wide range of biological activity displayed by this 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.[1,3,4] Also, benzo[*b*]-thiophene and its condensed analogues are important structural components in the development of optoelectronic materials, including organic photovoltaics and field effect transistors.[1b,5] Therefore, research directed toward a 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,e,f,6a,7−9] The methodology has also been extended to transition-metal-catalyzed cyclization of these analogues, 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 an intermolecular cross-coupling reaction of *o*-(*gem*-dibromovinyl)-thiophenols.[10e−g] The crucial bond-forming event in these reactions is intramolecular attack of the nucleophilic sulfur atom on the activated C−C multiple bond, leading to the formation of the S(1)−C(2) bond of the benzothiophene core. These reactions, although selective and efficient, however, require prior synthesis of difficult to access prefunctionalized thiophenol precursors.[9] Recently, copper-catalyzed (or Pd-catalyzed) double thiolation of *o*-(2-halovinyl)halobenzenes[11a] or 2-bromoalkynylbenzenes[11b] with metal sulfides or its surrogates,[11c−11d] 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 the S(1)−C(7a) bond formation via intramolecular C−S coupling/cyclization of α-arylthioenol/enolate precursors are scarce in the literature. One of the oldest syntheses, which falls under this category, involves iodine-[13] or chlorine-mediated[14] oxidative cyclization of β-aryl-α-mercaptoacrylic acids furnishing benzo-[*b*]thiophene-2-carboxylic acids in good yields.[15] Recently, Willis and co-workers described the 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-triarylethenethiols was 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 toward the development of new and efficient methods for five- and six-membered heterocycles employing novel organosulfur synthons,[18] we 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).

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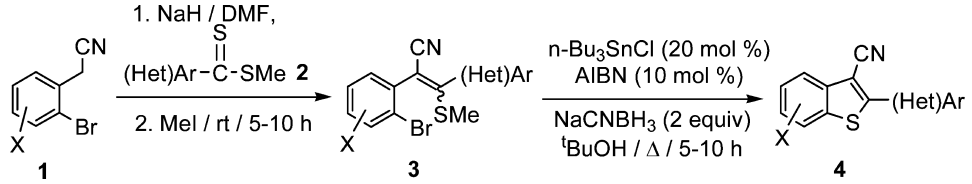
Scheme 1. Intramolecular Radical-Mediated Synthesis of Benzo[*b*]thiophenes



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

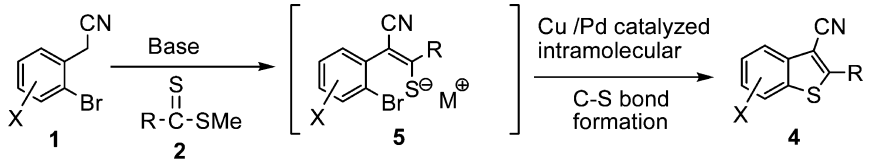
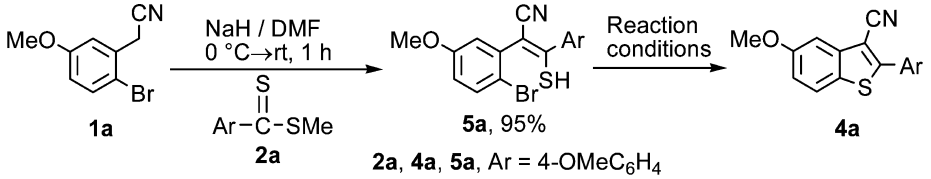


Table 1. Optimization of Reaction Conditions for the Formation of 4a from 5a



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

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 analogues 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.

Initially, 2-bromo-5-methoxyphenylacetonitrile (**1a**) and 4-methoxyphenyl dithioester (**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-catalzyed (or Pd-catalyzed) cyclization of enethiol intermediate **5a**, which was obtained in 95% yield by condensation of **1a** with **2a** in the presence of a base such as 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 such as 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 after prolonged heating (Table 1, entries 1 and 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 with heating for a prolonged time at 120 °C (Table 1, entries 3–6), with CuI displaying the 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

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ligand, and NaH as base in DMF as solvent when the reaction was complete within 3 h at 90 °C, furnishing the benzothiophene **4a** in 92% yield (entry 12). Decreasing the reaction temperature (entry 15) or catalytic loading (entry 16) or changing the CuI/ligand ratio (entries 17 and 18) required longer time for completion of the reaction without much affecting the yield of **4a** (Table 1).

Having accomplished the optimal conditions for intramolecular cyclization of **5a** to benzothiophene **4a**, we next aimed to combine the 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 h, 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, an aryl group of **1** bearing either the electron-donating or electron-withdrawing groups on the phenyl ring has little effect on the 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 a 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 and 8 and also 17 and 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** and **4n**, indolo[2,3-*b*]thiophenes **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 a 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 the 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)alkylaminobenzo/hetero-fused thiophenes **4s−w**, respectively, in high yields (entries 19−23). Similarly, the 2-(anilino)benzo[*o*]thiophene **4x** or the indolo-fused analogue **4y** could also be synthesized in good yields by using phenyl isothiocyanate as thiocarbonyl component (Table 2, entries 24 and 25).

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) an FT NMR spectrometer with $CDCl_3$ (or) DMSO-d_6 as solvent. Chemical shifts were reported in δ parts per million 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), quint (quintet), sext (sextet), dd (double of 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 an FT-IR instrument and HRMS on a 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**, and **2o**,**p** and the unknown dithioesters **2f−h** and **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** are 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; ^{1}H 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; ^{1}H 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; ^{1}H 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,

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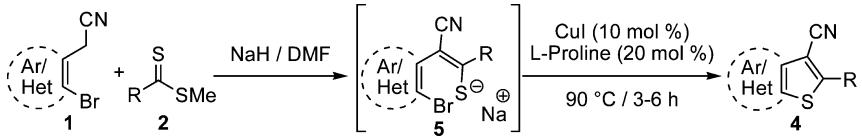
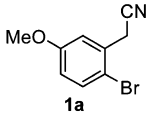
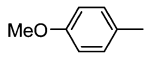
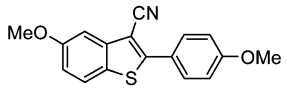
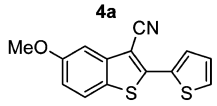
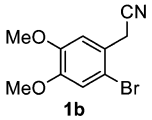
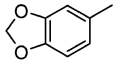
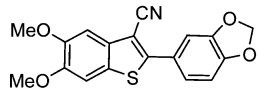
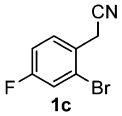
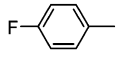
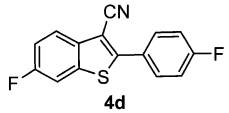
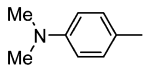
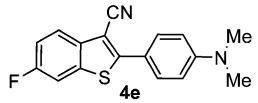
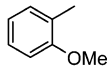
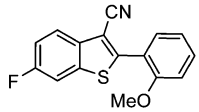
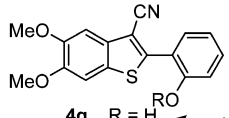
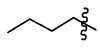
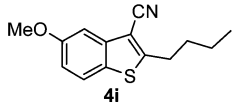
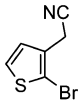
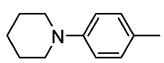
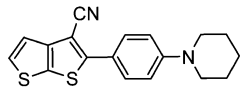
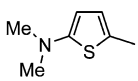
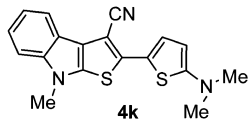
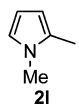
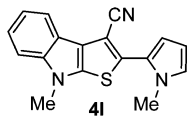
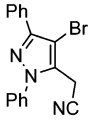
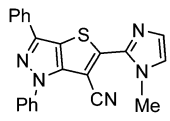
Table 2. Syntheses of 2,3-Substituted Benzo[*b*]- and Hetero-Fused Thiophenes 4



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 (TFA)	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

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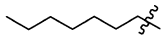
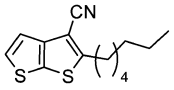
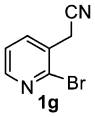
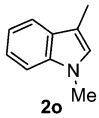
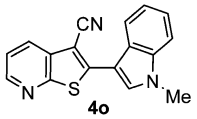
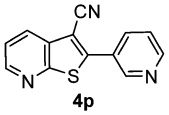
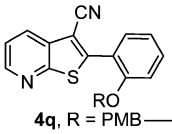
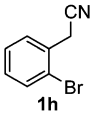
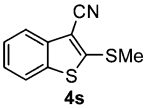
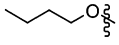
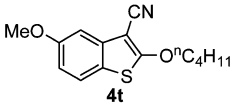
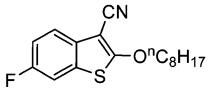
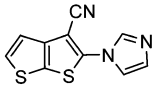
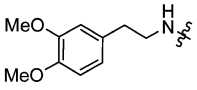
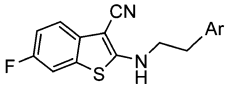
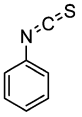
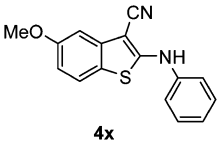
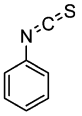
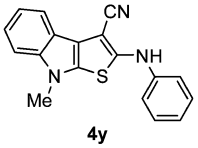
J. Org. Chem. 2015, 80, 2884−2892

Table 2. continued

entry	1	2, R	product	yield (%)[a]
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**

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 (quint, 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 the 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 of NaH (60% suspension in mineral oil) (80 mg, 2.0 mmol) in DMF (5 mL) at 0 °C. After being further stirred for 10 min, 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 saturated NH_4Cl solution (25 mL) and extracted with EtOAc (3 × 25 mL), and the combined organic layer was washed with water (3 × 25 mL) and brine

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J. Org. Chem. 2015, 80, 2884−2892

(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 semisolid (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) were added 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), and the reaction mixture was heated at 90 °C with constant stirring for 3 h (monitored by TLC). It was then diluted with saturated NH_4Cl solution (25 mL) and extracted with EtOAc (3 × 25 mL), and the combined organic layer was washed with water (3 × 25 mL) and 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 the 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 was added dropwise the corresponding 2-bromo(het)arylacetonitrile (**1a−h**) (1.0 mmol) in DMF (2 mL). After being further stirred for 10 min, a solution of either respective dithioester (**2a−p**) or thiocarbonyl 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 the 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 saturated NH_4Cl solution (25 mL) and extracted with EtOAc (3 × 25 mL), and the combined organic layer was washed with water (3 × 25 mL) and 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 and extracted with DCM (3 × 25 mL), and the combined organic layer was washed with water (3 × 25 mL) and 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 **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; ^1H 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; ^1H 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),

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3.11 (t, J = 7.6 Hz, 2H), 1.78 (quint, J = 7.2 Hz, 2H), 1.45 (sext, 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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**, gray 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; ^{1}H 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; ^{1}H 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; ^{1}H 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 (quint, J = 6.4 Hz, 2H), 1.53 (sext, 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; ^{1}H 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;

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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.

■ ASSOCIATED CONTENT

Supporting Information

Thirty 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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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Dr. Nitya Anand on his 90th birthday.

■ REFERENCES

(1) (a) Singh, P. P.; Yadav, A. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2009**, *74*, 5496 and references cited therein. (b) Gabriele, B.; Mancuso, R.; Lupinacci, E.; Veltri, L.; Salerno, G.; Carfagna, C. *J. Org. Chem.* **2011**, *76*, 8277 and references cited therein.

(2) (a) Hsiao, C.-N.; Kolasa, T. *Tetrahedron Lett.* **1992**, *33*, 2629. (b) Rossi, A.; Pergola, C.; Koeberle, A.; Hoffmann, M.; Dehm, F.; Bramanti, P.; Cuzzocrea, S.; Werz, O.; Sautebin, L. *Br. J. Pharmacol.* **2010**, *161*, 555.

(3) (a) Qin, Z.; Kastrati, I.; Chandrasena, R. E. P.; Liu, H.; Yao, P.; Petukhov, P. A.; Bolton, J. L.; Thatcher, G. R. J. *J. Med. Chem.* **2007**, *50*, 2682. (b) Schopfer, U.; Schoeffter, P.; Bischoff, S. F.; Nozulak, J.; Feuerbach, D.; Floersheim, P. *J. Med. Chem.* **2002**, *45*, 1399.

(4) (a) Liu, H.; Liu, J.; van Breeman, R. B.; Thatcher, G. R. J.; Bolton, J. L. *Chem. Res. Toxicol.* **2005**, *18*, 162. (b) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670.

(5) (a) Ohshita, J.; Lee, K.-H.; Kimura, K.; Kunai, A. *Organometallics* **2004**, *23*, 5622. (b) Ebata, H.; Miyazaki, E.; Yamamoto, T.; Takimiya, K. *Org. Lett.* **2007**, *9*, 4499. (c) Hari, D. P.; Hering, T.; Konig, B. *Org. Lett.* **2012**, *14*, 5334 and references cited therein. (d) Ota, S.; Minami, S.; Hirano, K.; Satoh, T.; Le, Y.; Seki, S.; Aso, Y.; Miura, M. *RSC Adv.* **2013**, *3*, 12356 and references cited therein. (e) Mori, T.; Nishimura, T.; Yamamoto, T.; Doi, I.; Miyazaki, E.; Osaka, I.; Takimiya, K. *J. Am. Chem. Soc.* **2013**, *135*, 13900 and references cited therein. (f) Ruzie, C.; Karpinska, J.; Kennedy, A. R.; Geerts, Y. H. *J. Org. Chem.* **2013**, *78*, 7741.

(6) Reviews: (a) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. For selected examples, see: (c) Wang, Z.; Geng, W.; Wang, H.; Zhang, S.; Zhang, W.-X.; Xi, Z. *Tetrahedron Lett.* **2011**, *52*, 6997 and references cited therein.

(7) (a) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651. (b) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377. (c) Bui, C. T.; Flynn, B. L. *J. Comb. Chem.* **2006**, *8*, 163. See also: (d) Danilkina, N. A.; Kulyashova, A. E.; Khlebnikova, A. E.; Brase, S.; Balova, I. A. *J. Org. Chem.* **2014**, *79*, 9018. (e) Sheng, J.; Fan, C.; Wu, J. *Chem. Commun.* **2014**, *50*, 5494.

(8) (a) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905. (b) Mehta, S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 1652.

(9) Sanz, R.; Guilarte, V.; Hernando, E.; Sanjuan, A. M. *J. Org. Chem.* **2010**, *75*, 7443.

(10) (a) Lu, W.-D.; Wu, M.-J. *Tetrahedron* **2007**, *63*, 356. (b) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473. (c) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 2649. (d) Newman, S. G.; Aureggi, V.; Bryan, C. S.; Lautens, M. *Chem. Commun.* **2009**, 5236. (e) Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064. (f) Zhou, W.; Chen, W.; Wang, L. *Org. Biomol. Chem.* **2012**, *10*, 4172. (g) Zeng, F.; Alper, H. *Org. Lett.* **2011**, *13*, 2868.

(11) (a) Li, C.-L.; Zhang, X.-G.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 7037. (b) Sun, L.-L.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G. *J. Org. Chem.* **2011**, *76*, 7546. (c) Guilarte, V.; Fernandez-Rodriguez, M. A.; Garcia-Garcia, P.; Hernando, E.; Sanz, R. *Org. Lett.* **2011**, *13*, 5100. (d) Prasad, D. J. C.; Sekar, G. *Org. Biomol. Chem.* **2013**, *11*, 1659. See also: (e) Shinamura, S.; Osaka, I.; Miyazaki, E.; Nakao, A.; Yamagishi, M.; Takeya, J.; Takimiya, K. *J. Am. Chem. Soc.* **2011**, *133*, 5024 and references cited therein.

(12) For other recent synthesis, see: (a) Kunz, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 1958. (b) Duan, Z.; Ranjit, S.; Liu, X. *Org. Lett.* **2010**, *12*, 2430. (c) Liu, K.; Jia, F.; Xi, H.; Li, Y.; Zheng, X.; Guo, Q.; Shen, B.; Li, Z. *Org. Lett.* **2013**, *15*, 2026. (d) Yang, D.; Yan, K.; Wei, W.; Tian, L.; Li, Q.; You, J.; Wang, H. *RSC Adv.* **2014**, *4*, 48547. (e) Kinfe, H. H.; Makolo, F. L.; Adokoh, C. K. *J. Org. Chem.* **2014**, *79*, 7718. (f) Reddy, C. R.; Dilipkumar, U.; Reddy, M. D. *Org. Lett.* **2014**, *16*, 3792.

(13) (a) Campaigne, E.; Cline, R. E. *J. Org. Chem.* **1956**, *21*, 39. (b) Campaigne, E.; Kreighbaum, W. E. *J. Org. Chem.* **1961**, *26*, 1326.

(14) (a) Chakrabarti, P. M.; Chapman, N. B.; Clarke, K. *Tetrahedron* **1969**, *25*, 2781. (b) Chakrabarti, P. M.; Chapman, N. B. *J. Chem. Soc. C* **1970**, 914.

(15) Allen, D.; Callaghan, O.; Cordier, F. L.; Dobson, D. R.; Harris, J. R.; Hotten, T. M.; Owton, W. M.; Rathmell, R. E.; Wood, V. A. *Tetrahedron Lett.* **2004**, *45*, 9645.

(16) (a) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Tetrahedron* **2006**, *62*, 11513. See also: (b) Yoshida, S.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 5573.

(17) Inamoto, K.; Arai, Y.; Hiroya, K.; Doi, T. *Chem. Commun.* **2008**, 5529.

DOI: 10.1021/acs.joc.5b00032
J. Org. Chem. 2015, 80, 2884−2892

(18) Review: (a) Ila, H.; Junjappa, H. *Chimia* **2013**, *67*, 17. Recent papers: (b) Acharya, A.; Vijay Kumar, S.; Saraiah, B.; Ila, H. *J. Org. Chem.* **2015**, *80*, 414. (c) Vijay Kumar, S.; Saraiah, B.; Parameshwarappa, G.; Ila, H.; Verma, G. K. *J. Org. Chem.* **2014**, *79*, 7961. (d) Raghava, B.; Parameshwarappa, G.; Acharya, A.; Swaroop, T. R.; Rangappa, K. S.; Ila, H. *Eur. J. Org. Chem.* **2014**, 1882. (e) Yugandar, S.; Acharya, A.; Ila, H. *J. Org. Chem.* **2013**, *78*, 4960. (f) Yugandar, S.; Misra, N. C.; Parameshwarappa, G.; Panda, K.; Ila, H. *Org. Lett.* **2013**, *15*, 5250. (g) Vijay Kumar, S.; Parameshwarappa, G.; Ila, H. *J. Org. Chem.* **2013**, *78*, 7362. (h) Vijay Kumar, S.; Yadav, S. K.; Raghava, B.; Saraiah, B.; Ila, H.; Rangappa, K. S.; Hazra, A. *J. Org. Chem.* **2013**, *78*, 4960. (i) Vijay Kumar, S.; Saraiah, B.; Misra, N. C.; Ila, H. *J. Org. Chem.* **2012**, *77*, 10752.

(19) Singh, P. P.; Yadav, A. K.; Ila, H.; Junjappa, H. *Eur. J. Org. Chem.* **2010**, 338.

(20) Rudorf, W.-D.; Schierhorn, A.; Augustin, M. *J. Prakt. Chem.* **1979**, *321*, 1021.

(21) (a) Ramadas, S. R.; Srinivasan, P. S.; Ramachandran, J.; Sastry, V. V. S. K. *Synthesis* **1983**, 605. (b) Singh, G.; Bhattacharjee, S. S.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 693. (c) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. In *Vogel's Textbook of Practical Organic Chemistry*; Vogel, A. I., Ed.; Wiley: New York, 1989; Chapter 5, pp 792−794. (d) Mohanta, P. K.; Dhar, S.; Samal, S. K.; Ila, H.; Junjappa, H. *Tetrahedron* **2000**, *56*, 629. (e) Hodgkins, J. E.; Reeves, W. B. *J. Org. Chem.* **1964**, *29*, 3098.

DOI: 10.1021/acs.joc.5b00032
J. Org. Chem. 2015, 80, 2884−2892