ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

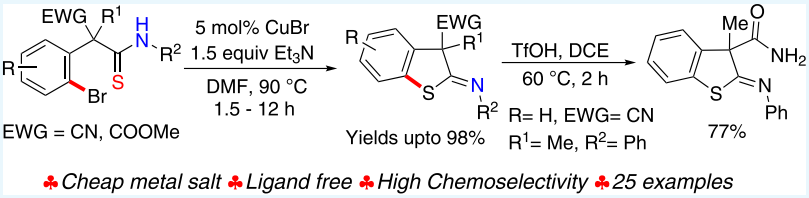
Chemoselective Ullmann Reaction of α-Trisubstituted Thioamides: Synthesis of Novel 2-Iminobenzothiolanes

Anwesha Bhattacharya, Annaram Thirupathi, Pradeep Natarajan, and Saravanan Peruncheralathan*

Cite This: *ACS Omega* 2021, 6, 21169−21180

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: New classes of unexplored benzo[*b*]thiolanes are synthesized from trisubstituted thioamides through copper-catalyzed intramolecular *S*-arylation of thioamides for the first time. This method provides good to excellent yields with fully controlled chemoselectivity. Unusually, iminobenzo[*b*]thiolanes are very stable under mild acidic conditions. A plausible mechanism is proposed for the chemoselective *S*-arylation process.

INTRODUCTION

Benzothiophene is a predominant structural core compound in drugs and device materials.[1−4] In particular, 2-aminobenzothiophenes show various biological activities, such as acetyl-CoA carboxylase inhibitor, tubulin polymerization, and mycobacterium inhibition.[5] They are also precursors for the synthesis of the well-known drug raloxifene and its analogues.[6] Therefore, several elegant synthetic methods have been developed for the construction of 2-aminobenzothiophene derivatives,[7] whereas those for the 2-iminobenzothiophene core remain elusive in the literature.[8,9] Recently, a 2-iminothiophene-fused polyaromatic compound **A** were synthesized from thioamides (Figure 1).[10] The photophysical studies show emission in the range of 500−606 nm with quantum yields up to 0.64.[10] Hence, compound **A** has been considered a potential core for developing optical device materials. Furthermore, the 2-aminobenzothiolane core is found in marine alkaloid makaluvamine F, which has potent cytotoxicity.[11] Hydrolysis of 2-iminobenzothiophenes **1** provides unknown classes of 2-oxobenzothiolanes **2** (Figure 1).[12] They are *S*-analogues of 2-oxindole derivatives. The indole derivatives are found in numerous natural products such as horsfiline, a 3,3′-spiro-2-oxindole alkaloid, alstonisine, gelsemine, and spirotryprostatin B.[12] Until now, the synthesis of 2-oxobenzothiolanes has not been reported, whereas synthesis of benzothiolane and its 3-oxo derivatives is well developed.[11a,13,14] Hence, developing a new protocol to synthesize 2-iminobenzothiolanes and their 2-oxo derivatives is highly desirable for therapeutic and materials science applications.

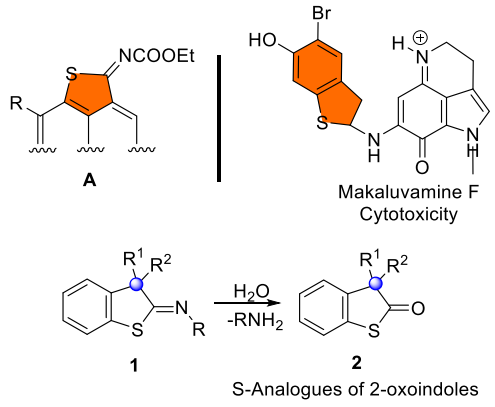
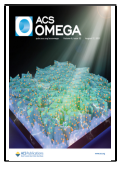


Figure 1. Selected 2-imino-fused thiophenes and 2-aminobenzo[*b*]-thiolane.

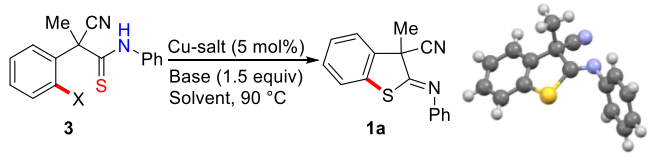
Thioamides are versatile synthons and are extensively used in the synthesis of heterocyclic building blocks.[15] Notably, a wide range of thiazoles and their benzo derivatives is synthesized by inter/intramolecular *S*-alkylation and arylation of appropriate thioamides with the respective electrophilic partners.[16,17] They proceed through either metal or metal-free reaction conditions. Similarly, thiophenes are prepared from thioamides and biselectrophiles.[18] However, thioamides are rarely employed as reactive partners to synthesize 2-aminobenzothiophenes compared to benzothiazole synthesis.[19] The chemoselective *S*-arylation of thioanilides has significant

Received: June 30, 2021
Accepted: July 27, 2021
Published: August 4, 2021



https://doi.org/10.1021/acsomega.1c03410
ACS Omega 2021, 6, 21169−21180

Table 1. Optimization of *S*-Arylation of α-Trisubstituted Thioamide 3



entry	3	Cu salt	base	solvent	temp (°C)	time (h)	yield (%)[a]
1.	X = Br	CuI	KO^{t}Bu	DMF	Rt	4	20[b]
2.	X = Br	CuI	KO^{t}Bu	DMF	60	3	42[b]
3.	X = Br	CuI	KO^{t}Bu	DMF	90	3	68[b]
4.	X = Br	CuI	KO^{t}Bu	DMF	90	3	77
5.	X = Br	CuI	Cs_2CO_3	DMF	90	3	77
6.	X = Br	CuI	K_3PO_4	DMF	90	3	85
7.	X = Br	CuI	Et_3N	DMF	90	3	91
8.	X = Br	CuI	K_2CO_3	DMF	90	3	69
9.	X = Br	CuI	Et_3N	toluene	90	3	91
10.	X = Br	CuI	Et_3N	dioxane	90	3	86
11.	X = Br	CuI	Et_3N	DMSO	90	3	92
12.	**X = Br**	**CuBr**	**Et_3N**	**DMF**	**90**	**1.5**	**98**
13.	X = Br	CuCl	Et_3N	DMF	90	1.5	92
14.	X = Br	$Cu(OAc)_2$	Et_3N	DMF	90	1.5	95
15.	X = I	CuBr	Et_3N	DMF	90	4	82
16.	X = Cl	CuBr	Et_3N	DMF	90	10	20
17.	X = Br	CuBr	Et_3N	DMF	90	2	83[c]

[a]Isolated yields. [b]With 1,10-phenanthroline ligand (10 mol %). [c]TEMPO (1 equiv) was used, TEMPO-(2,2,6,6-Tetramethylpiperidin-1-yl)ox.

limitations. Recently, Olofsson and co-workers reported intermolecular chemoselective *S*-arylation of thioamides with diaryliodonium salts affording arylthioimidates.[20] We recently reported copper-catalyzed intramolecular *S*-arylation of thioamides at room temperature providing 2-aminobenzothiophenes in good to excellent yields.[21] Due to our ongoing interest in chemoselective heterocycle synthesis,[22] herein we wish to report a chemoselective Ullmann reaction of α-trisubstituted thioamides under ligand-free conditions affording new classes of 2-iminobenzothiolanes for the first time.

RESULTS AND DISCUSSION

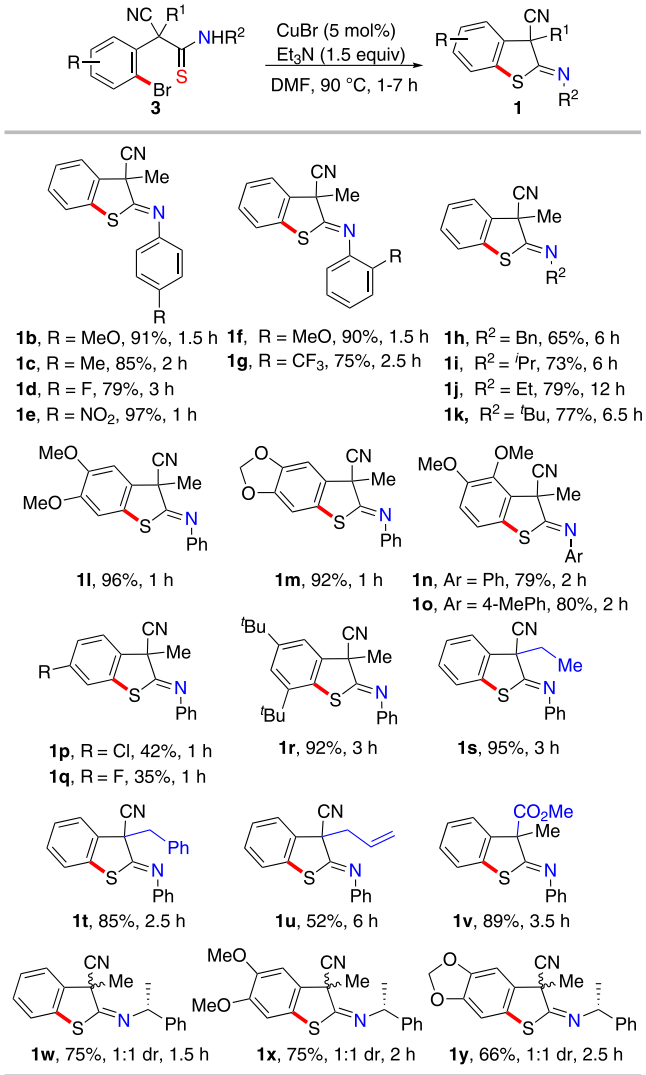
The required trisubstituted thioamides **3** were prepared from α-(2-bromoaryl)-propanenitriles **4** or α-(2-bromophenyl)-propanoate **6** and aromatic/alkyl isothiocyanates **5** in the presence of NaHMDS affording the corresponding thioamides **3a−y** in moderate to good yields (Table S1, Supporting Information). Spectral and analytical data characterized all newly synthesized 2-(2-bromoaryl)-2-cyano/carbmethoxy-*N*-substituted propanethioamide derivatives **3a−y**. Having all the thioamides **3a−y**, we started to investigate the suitable conditions for a chemoselective intramolecular *S*-arylation process. Hence, thioamide **3a** was chosen as the model substrate for this process. The optimization began with CuI, KO^{t}Bu, and 1,10-phenanthroline at room temperature. The reaction was sluggish and afforded only 20% of the benzo[*b*]thiolane derivative **1a** (Table 1, entry 1). Keeping the rest of the conditions the same, the reaction at different temperatures was studied. When the reaction was carried out at 60 °C, the yield of benzo[*b*]thiolane **1a** increased to 42% (Table 1, entry 2). Subsequently, the reaction temperature was further raised to 90 °C, and the yield enhanced to 68% (Table 1, entry 3).

When the reaction was carried out in the absence of a ligand, to our surprise, thioamide **3a** yielded 77% of product **1a** (Table 1, entry 4). This indicates that the ligand did not affect the *S*-arylation process. The structure of **1a** was also confirmed by single-crystal X-ray analysis (Table 1). To improve the reaction's efficiency, we screened different bases such as Cs_2CO_3, K_3PO_4, Et_3N, and K_2CO_3, out of which Et_3N gave 91% of benzo[*b*]thiolane **1a** (Table 1, entries 5−8). Furthermore, we screened solvents like toluene, dioxane, and dimethyl sulfoxide (DMSO) (Table 1, entries 9−11). Only DMSO gave a comparable yield to that of DMF. Next, copper salts were tested for optimization, such as CuCl, CuBr, and $Cu(OAc)_2$. We found that CuBr yielded 98% of **1a** (Table 1, entries 12−14). Instead of aryl bromide, iodo and chloro derivatives were also examined. Aryl iodide gave 82% of benzo[*b*]thiolane **1a** (Table 1, entry 15), whereas only 20% of **1a** was observed after 10 h in the case of a chloro derivative (Table 1, entry 16). We did not find any trace amount of the *N*-arylated product during the optimization studies. In the presence of the radical scavenger TEMPO, we obtained 83% of benzo[*b*]thiolane **1a** (Table 1, entry 17). This indicates that the *S*-arylation process does not proceed through a radical path.

The optimized reaction conditions were tested on the various trisubstituted thioamides **3b−y**. Initially, *N*-aryl-substituted thioamides **3b−g** were studied. The electron-donating groups on *N*-phenyl derivatives **3b,c** gave the corresponding benzo[*b*]thiolanes **1b,c** in 85−91% yields (Table 2). Similarly, the *para*-fluoro- and nitro-substituted *N*-phenyl thioamides **3d,e** were smoothly transformed to benzo[*b*]thiolanes **1d,e** in good to excellent yields (Table 2). The reaction was continued with *ortho*-substituted thioanilides **3f,g**. The benzo[*b*]thiolanes **1f,g** were obtained from the respective thioanilides **3f,g** in 75−90% yields (Table 2). Next, we examined alkyl-substituted thioamides **3h−k** under the optimized reaction conditions. The *S*-arylation of thioamides **3h−k** took a bit longer reaction time of about 6−12 h to afford

https://doi.org/10.1021/acsomega.1c03410
ACS Omega 2021, 6, 21169−21180

Table 2. Scope of the Copper-Catalyzed *S*-Arylation of α-Trisubstituted Thioamides 3b−y[a]

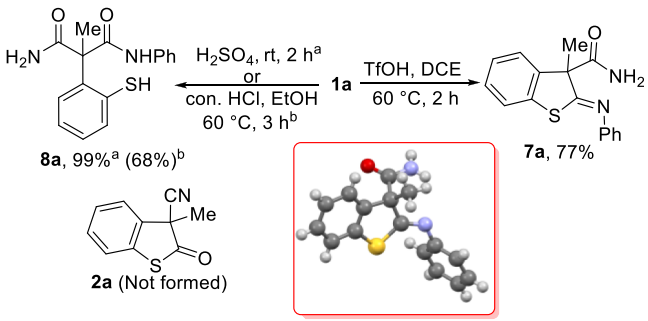


[a]Isolated yields.

the corresponding benzo[*b*]thiolanes **1h−k** in good to excellent yields (Table 2). Furthermore, we investigated the electron-donating group on 2-bromoaryl derivatives **3l−o**. These derivatives **3l−o** underwent a smooth *S*-arylation process yielding benzo[*b*]thiolanes **1l−o** in good to excellent yields (Table 2). However, the halo-substituted thioamides **3p,q** gave the *S*-arylated products **1p,q** in 35−42% yields (Table 2). Interestingly, the sterically hindered arylbromo derivative **3r** gave rise to benzo[*b*]thiolane **1r** in 92% yield (Table 2). Next, we changed the methyl group at the α-trisubstituted thioamide to ethyl, benzyl, and allyl groups. Thus, ethyl- and benzyl-substituted thioamide derivatives **3s,t** yielded the corresponding benzo[*b*]thiolanes **1s,t** in 85−95% yields (Table 2). However, the allyl derivative **3u** gave only 52% yield of the *S*-arylated product **1u** and took a longer reaction time (Table 2). The ester motif-containing trisubstituted thioamide **3v** was studied under identical conditions. The ester-containing benzo[*b*]thiolane **1v** was obtained in 89% yield in 3.5 h (Table 2). Next, we focused our attention on synthesizing enantiomerically pure benzo[*b*]thiolanes from chiral α-trisubstituted thioamides. The chiral α-trisubstituted thioamides **3w−y** were prepared in moderate to good yields with 1:1 diastereoisomers (Table S1, Supporting Information). The thioamides **3w−y** were subjected to optimized conditions affording 2-iminobenzo[*b*]thiolanes **1w−y** in 66−75% yields (Table 2).

Finally, we attempted to synthesize *S*-analogues of 2-oxindole derivatives. Thus, newly synthesized 2-iminobenzo-[*b*]thiolane **1a** was subjected to hydrolysis conditions; to our surprise, the imine functionality was relatively rigid to hydrolysis. The 2-iminobenzo[*b*]thiolane **1a** was subjected to 10 equivalents of triflic acid at 60 °C, resulting in the hydrolysis of the nitrile moiety. The imine functionality remained intact. The structure of **7a** was also confirmed by single-crystal X-ray analysis (Scheme 1). However, **1a** was

Scheme 1. Hydrolysis of Benzo[*b*]thiolane 1a



subjected to concentrated H_2SO_4 under a neat condition, which resulted in the cleavage of the heterocycle and hydrolysis of nitrile and imine functionalities yielding 2-(2-mercaptophenyl)-2-methyl-*N*-phenylmalonamide **8a** in a quantitative yield (Scheme 1). A similar result was observed in the presence of conc. HCl. However, **8a** was obtained in 68% yield (Scheme 1). Furthermore, our attempts to reduce the imine moiety of **1a** failed.[23]

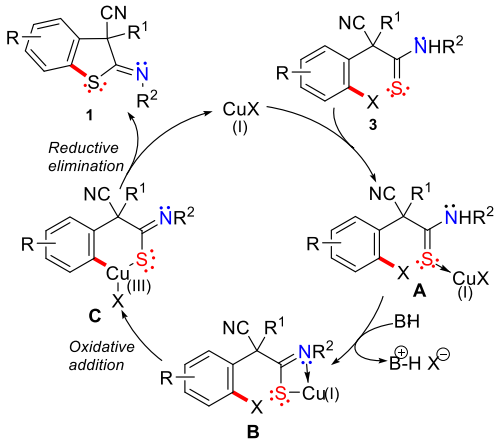
To understand the chemoselective *S*-arylation process mechanism, as aforementioned the *S*-arylation process proceeds through an ionic pathway instead of a radical path (Table 1, entry 17). The *S*-center of thioamide is more nucleophilic than the *N*-center. Hence, first, thioamide **3** forms a coordinate complex **A** with the copper salt. In a base, complex **A** is transformed to the copper(I)thiolate complex **B**, which is also stabilized by *N*-center coordination. Next, complex **B** undergoes an intramolecular oxidative addition affording the copper(III) complex **C**. This step is crucial, which is influenced by the nature of aryl halides and nitrogen substituents. Finally, the complex **C** undergoes reductive elimination to afford the *S*-arylated product **1** and regenerated the Cu(I) catalyst (Scheme 2). The oxidative addition of 2-chlorophenyl derivative **3z** is slow and less efficient; hence, a lower yield of **1a** was observed (Table 1, entry 15). Electron-deficient 2-bromoaryl thioamides **3p,q** undergo a slow oxidative addition process; therefore, lower yields were obtained (Table 2). Electron-rich *N*-alkyl thioamides **3h−k** form a strong coordinate complex **B**. Thus, these complexes require a longer reaction time to complete the oxidative process.

CONCLUSIONS

We have demonstrated a simple approach for synthesizing unexplored 2-imino-3,3′-alkylcyanobenzo[*b*]thiolanes via the

https://doi.org/10.1021/acsomega.1c03410
ACS Omega 2021, 6, 21169−21180

Scheme 2. Plausible Mechanism for the Formation of Benzo[*b*]thiolane 1



copper-catalyzed *S*-arylation of α-trisubstituted thioamides for the first time. This catalytic process is highly chemoselective. We have prepared a series of all-carbon quaternary-centered 2-iminobenzo[*b*]thiolanes in good to excellent yields. Interestingly, we found that the 2-imino moiety is very stable under mild acidic conditions, whereas the thiolane ring was cleaved under a neat acidic condition. Overall, we demonstrated that the Ullmann reaction is a powerful tool for synthesizing a new class of *S*-heterocycles without using any ligands. Currently, the application of 3,3′-disubstituted-2-iminobenzothiolanes is undergoing in our laboratory.

EXPERIMENTAL SECTION

General Information. All reactions were performed using the standard vial technique with a rubber septum. All solids were weighed in air. Dioxane, Cs_2CO_3, K_3PO_4, KO^{t}Bu, and K_2CO_3 were purchased from Aldrich, Acros, Merck, Spectrochem, or Alfa Aesar and used as received. CuI, CuBr, CuCl, Cu(OAc)$_2$, and 1,10-phenanthroline were purchased from Aldrich. Dried DMF, DMSO, toluene, and Et_3N were used. Isothiocyanates were synthesized from substituted anilines, and few isothiocyanates were purchased from Aldrich. All other reagents were purchased from common suppliers and used without further purification. Flash chromatography was performed using a Merck silica gel (230−400 mesh). Fractions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F_{254} plates (Merck & Co.) and were visualized by a UV light. Nuclear magnetic resonance (NMR) spectroscopy data were recorded using Bruker ARX 400 and 700 spectrometers. ^{13}C and ^{1}H NMR spectra were recorded in $CDCl_3$ and CD_3SOCD_3 referenced according to signals of deutero solvents. Electrospray ionization high-resolution mass spectrometry (ESI HR-MS) measurements were performed using a Bruker micrOTOF-Q II mass-spectrometer.

General Procedure for the Synthesis of Thioamides 3a−aa. To a stirring suspension of corresponding 2-(2-bromoaryl)propanenitriles[24] (6.0 mmol, 1.0 equiv) in THF, NaHMDS (1.0 M in THF) was added dropwise at 0 °C. After being further stirred for 15 min at room temperature, a solution of isothiocyanates (6.6 mmol, 1.2 equiv) in THF was added to the reaction mixture at 0 °C followed by further stirring for 15−45 min at room temperature. After the starting materials (monitored by TLC) were completely consumed, the reaction mixture was quenched with a saturated NH_4Cl solution and extracted with ethyl acetate (EtOAc). The combined organic layer was washed with water (3 × 25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated under a reduced pressure. The crude products were purified by flash chromatography using hexane and EtOAc as the eluents.

*2-(2-Bromophenyl)-2-cyano-N-phenylpropanethioamide (**3a**).* Yield: 75% (0.258 g); pale yellow solid; R_f: 0.35 in 30% EtOAc in hexanes; mp: 124−125 °C; IR (ν cm^{-1}) =2974, 2362, 2243, 1530, 1406, 1344, 1160, 1036, 1004, 808, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.42 (t, J = 8.0 Hz, 2H), 7.34−7.29 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 138.1, 135.5, 135.2, 131.1, 129.4, 129.2, 128.0, 127.7, 124.6, 124.4, 119.7, 56.7, 29.6. HR-MS (ESI-TOF) *m/z*: cal. for $C_{16}H_{13}BrN_2S$ [M + H]$^+$: 345.0056 and 347.0044; found: 345.0051 and 347.0035.

*2-(2-Bromophenyl)-2-cyano-N-(4-methoxyphenyl)-propanethioamide (**3b**).* Yield: 91% (0.340 g); pale yellow solid; R_f: 0.32 in 30% EtOAc in hexanes; mp: 127−129 °C; IR (ν cm^{-1}) = 3628, 3306, 2352, 1732, 1698, 1656, 1564, 746; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 10.73 (s, 1H), 7.77 (d, J = 7.6 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 3.76 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 199.1, 158.3, 136.4, 135.0, 132.7, 131.4, 131.0, 128.7, 127.3, 124.6, 120.7, 114.2, 57.5, 55.7, 27.8. HR-MS (ESI-TOF) *m/z*: cal. for $C_{17}H_{15}BrN_2OS$ [M + H]$^+$: 375.0161 and 377.0146; found: 375.0166 and 377.0141.

*2-(2-Bromophenyl)-2-cyano-N-(p-tolyl)propanethioamide (**3c**).* Yield: 73% (0.261 g); pale yellow solid; R_f: 0.30 in 30% EtOAc in hexanes; mp: 180−182 °C; IR (ν cm^{-1}) = 3427, 2362, 1638, 1517, 1371, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 8.4 Hz, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 2.36 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 137.8, 135.7, 135.5, 135.2, 130.9, 129.8, 129.4, 128.2, 124.6, 124.3, 119.8, 56.44, 28.7, 21.2. HR-MS (ESI-TOF) *m/z*: cal. for $C_{17}H_{15}BrN_2S$ [M + H]$^+$: 359.0212 and 361.0192; found: 359.0227 and 361.0206.

*2-(2-Bromophenyl)-2-cyano-N-(4-fluorophenyl)-propanethioamide (**3d**).* Yield: 68% (0.261 g); pale yellow solid; R_f: 0.30 in 30% EtOAc in hexanes; mp: 139−141 °C; IR (ν cm^{-1}) = 3308, 1700, 1507, 1413, 1217, 833, 769; ^{1}H NMR (400 MHz, $CDCl_3$) 7.74−7.69 (m, 2H), 7.54 (s, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.46−7.43 (m, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.06 (t, J = 8.4 Hz, 2H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 160.1 (d, J = 245.2 Hz), 135.2, 134.1, 132.6 (d, J = 3.0 Hz), 131.1, 129.1, 128.4, 123.7, 122.7 (d, J = 8.0 Hz), 119.4, 115.9 (d, J = 22.5 Hz), 50.1, 24.2; ^{19}F NMR (376 Hz, $CDCl_3$) δ −116.23; HR-MS (ESI-TOF) *m/z*: cal. for $C_{16}H_{12}BrFN_2S$ [M + H]$^+$: 384.9781 and 386.9751; found: 384.9770 and 386.9760.

*2-(2-Bromophenyl)-2-cyano-N-(4-nitrophenyl)-propanethioamide (**3e**).* Yield: 70% (0.271 g); R_f: 0.26 in 30% EtOAc in hexanes; mp: 185−187 °C; IR (ν cm^{-1}) = 3303, 2927, 2362, 1336, 756, 667. ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 11.23 (s, 1H), 8.29 (d, J = 8.8 Hz, 2H), 7.80−7.78 (m, 4H), 7.59 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 200.8, 145.7, 145.6, 136.2, 135.1, 131.6, 131.1, 128.8, 126.6,

https://doi.org/10.1021/acsomega.1c03410
ACS Omega 2021, 6, 21169−21180

124.7, 124.6, 120.4, 58.0, 27.7. HR-MS (ESI-TOF) *m/z*: cal. for $C_{16}H_{12}BrN_3O_2S$ $[M + H]^+$: 389.9914 and 391.9895; found: 389.9906 and 391.9886.

*2-(2-Bromophenyl)-2-cyano-N-(2-methoxyphenyl)-propanethioamide (**3f**)*. Yield: 75% (0.280 g); yellow solid; R_f: 0.32 in 30% EtOAc in hexanes; mp: 154−156 °C; IR (ν cm^{-1}) = 3628, 3306, 2352, 1732, 1698, 1656, 1564, 746; ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.91 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 3.78 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 150.1, 135.7, 135.2, 130.8, 129.4, 127.98, 127.80, 127.2, 125.1, 121.4, 120.5, 119.7, 110.5, 57.8, 56.1, 28.7. HR-MS (ESI-TOF) *m/z*: cal. for $C_{17}H_{15}BrN_2OS$ $[M + H]^+$: 375.0161 and 377.0139; found: 375.0161 and 377.0141.

*2-(2-Bromophenyl)-2-cyano-N-(2-(trifluoromethyl)-phenyl)propanethioamide (**3g**)*. Yield: 75% (0.309 g); yellow solid; R_f: 0.26 in 30% EtOAc in hexanes; mp: 200−202 °C; IR (ν cm^{-1}) = 3207, 3006, 2349, 2253, 1505, 1450, 1319, 1125, 746, 675; ^1H NMR (700 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.67−7.63 (m, 2H), 7.50 (t, J = 7.7 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.35 (t, J = 7.7 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 199.5, 135.9 (q, J = 1.22 Hz), 135.3, 135.2, 132.7, 131.2, 129.1, 128.8, 128.2, 128.0, 126.6 (q, J = 5.0 Hz), 125.0, 124.9 (q, J = 30.1 Hz), 123.3 (q, J = 271.7 Hz), 119.4, 57.1, 28.3; ^{19}F NMR (376 Hz, $CDCl_3$) δ −60.88. HR-MS (ESI-TOF) *m/z*: cal. for $C_{17}H_{12}BrF_3N_2S$ $[M + H]^+$: 412.9929 and 414.9903; found: 412.9918 and 414.9909.

*N-Benzyl-2-(2-bromophenyl)-2-cyanopropanethioamide (**3h**)*. Yield: 60% (0.215 g); pale yellow solid; R_f: 0.28 in 30% EtOAc in hexanes; mp: 148−150 °C; IR (ν cm^{-1}) = 3253, 2359, 1588, 1558, 1513, 1373, 1202, 1029, 748, 638, 502; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.39−7.29 (m, 5H), 4.87 (s, 1H), 4.88 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 135.5, 135.3, 135.1, 130.8, 129.2, 129.0, 128.4, 128.3, 128.1, 124.5, 119.6, 55.5, 51.1, 28.7. HR-MS (ESI-TOF) *m/z*: cal. for $C_{17}H_{15}BrN_2S$ $[M + H]^+$: 359.0212 and 361.0168; found: 359.0192 and 361.0192.

*2-(2-Bromophenyl)-2-cyano-N-isopropylpropanethioamide (**3i**)*. Yield: 56% (0.174 g); pale yellow solid; R_f: 0.30 in 30% EtOAc in hexanes; mp: 133−135 °C; IR (ν cm^{-1}) = 3744, 3303, 2961, 2347, 1735, 1700, 1656, 1559, 833, 647; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 4.66−4.58 (m, 1H), 2.21 (s, 3H), 1.28 (d, J = 6.0 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 135.6, 134.9, 130.7, 129.2, 127.9, 124.5, 119.6, 55.4, 48.5, 28.7, 20.9, 20.5. HR-MS (ESI-TOF) *m/z*: cal. for $C_{13}H_{15}BrN_2S$ $[M + H]^+$: 311.0212 and 313.0185; found: 311.0207 and 313.0192.

*2-(2-Bromophenyl)-2-cyano-N-ethylpropanethioamide (**3j**)*. Yield: 64% (0.190 g); yellow solid; R_f: 0.28 in 30% EtOAc in hexanes; mp: 122−124 °C; IR (ν cm^{-1}) = 3628, 2934, 2362, 2339, 1611, 1561, 1438, 1420, 1004, 665. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.46 (t, J = 6.8 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 3.74 (q, J = 6.4 Hz, 2H), 2.24 (s, 3H), 1.30 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 135.6, 135.0, 130.7, 129.2, 128.0, 124.5, 119.7, 55.4, 41.8, 28.7, 12.5. HR-MS (ESI-TOF) *m/z*: cal. for $C_{12}H_{13}BrN_2S$ $[M + H]^+$: 297.0056 and 299.0037; found: 297.0058 and 299.0035.

*2-(2-Bromophenyl)-N-(tert-butyl)-2-cyanopropanethioamide (**3k**)*. Yield: 58% (0.188 g); yellow solid; R_f: 0.28 in 30% EtOAc in hexanes; mp: 128−130 °C. IR (ν cm^{-1}) = 2969, 2934, 2867, 2238, 1651, 1472, 1130, 987, 756, 439; ^1H NMR (700 MHz, $CDCl_3$) δ 7.69 (d, J = 9.1 Hz, 1H), 7.59 (s, 1H), 7.56 (d, J = 9.1 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H), 7.31 (t, J = 8.4 Hz, 1H), 2.24 (s, 3H), 1.57 (s, 9H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 196.1, 135.8, 134.9, 130.6, 129.3, 127.9, 124.7, 119.9, 56.9, 56.6, 28.9, 27.0. HR-MS (ESI-TOF) *m/z*: cal. for $C_{14}H_{17}BrN_2S$ $[M + H]^+$: 325.0369 and 327.0355; found: 325.0377 and 327.0348.

*2-(2-Bromo-4,5-dimethoxyphenyl)-2-cyano-N-phenylpropanethioamide (**3l**)*. Yield: 73% (0.295 g); pale yellow solid; R_f: 0.32 in 30% EtOAc in hexanes; mp: 222−224 °C; IR (ν cm^{-1}) = 3447, 2253, 1517, 1467, 1299, 1004, 741; ^1H NMR (400 MHz, CD_3SOCD_3) δ 10.60 (s, 1H), 7.46−7.35 (m, 4H), 7.33 (s, 1H), 7.32−7.27 (m, 1H), 7.24 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 200.1, 150.3, 148.4, 139.8, 129.0, 127.7, 127.5, 126.2, 120.8, 117.9, 115.4, 114.6, 58.1, 56.5, 56.3, 28.2. HR-MS (ESI-TOF) *m/z*: cal. for $C_{18}H_{17}BrN_2O_2S$ $[M + H]^+$: 405.0267 and 407.0230; found: 405.0253 and 407.0247.

*2-(6-Bromo-3,4-methylenedioxyphenyl)-2-cyano-N-phenylpropanethioamide (**3m**)*. Yield: 72% (0.280 g); yellow solid; R_f: 0.31 in 30% EtOAc in hexanes; mp: 174−176 °C; IR (ν cm^{-1}) = 3450, 2349, 1529, 1395, 1256, 1004, 735; ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.39−7.27 (m, 2H), 7.27−7.19 (m, 1H), 7.13 (d, J = 8.8 Hz, 1H), 6.07 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 149.2, 148.1, 138.0, 129.2, 128.4, 127.8, 124.5, 119.8, 116.2, 114.9, 109.4, 102.7, 56.6, 29.2. HR-MS (ESI-TOF) *m/z*: cal. for $C_{17}H_{13}BrN_2O_2S$ $[M + H]^+$: 388.9954 and 390.9917; found: 388.9938 and 390.9934.

*2-(6-Bromo-2,3-dimethoxyphenyl)-2-cyano-N-phenylpropanethioamide (**3n**)*. Yield: 73% (0.295 g); pale yellow solid; R_f: 0.31 in 30% EtOAc in hexanes; mp: 174−176 °C; IR (νcm^{-1}) = 3450, 2240, 1723, 1518, 1456, 1290, 1012, 736; ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.48−7.32 (m, 3H), 7.29−7.24 (m, 1H), 6.83 (d, J = 8.8 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 153.3, 150.1, 138.4, 130.5, 129.4, 129.1, 127.6, 124.4, 121.0, 114.0, 113.6, 61.6, 56.1, 55.6, 29.4. HR-MS (ESI-TOF) *m/z*: cal. for $C_{18}H_{17}BrN_2O_2S$ $[M + H]^+$: 405.0267 and 407.0236; found: 405.0251 and 407.0247.

*2-(6-Bromo-2,3-dimethoxyphenyl)-2-cyano-N-(p-tolyl)-propanethioamide (**3o**)*. Yield: 70% (0.293 g); yellow solid; R_f: 0.30 in 30% EtOAc in hexanes; mp: 146−148 °C; IR (ν cm^{-1}) = 3447, 2237, 1732, 1517, 1467, 1299, 1004, 741, 656; ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 2.44 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 153.3, 150.0, 137.7, 135.8, 130.5, 129.7, 129.4, 124.4, 121.1, 113.9, 113.7, 61.6, 56.2, 55.6, 29.5, 21.3. HR-MS (ESI-TOF) *m/z*: cal. for $C_{19}H_{19}BrN_2O_2S$ $[M + H]^+$: 419.0423 and 421.0420; found: 419.0434 and 421.0403.

*2-(2-Bromo-4-chlorophenyl)-2-cyano-N-phenylpropanethioamide (**3p**)*. Yield: 65% (0.246 g); pale yellow solid; R_f: 0.31 in 30% EtOAc in hexanes; mp: 129−131 °C; IR (ν cm^{-1}) = 3442, 2362, 2238, 1641, 1520, 670; ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.71 (s, 1H), 7.60 (d, J = 7.6 Hz, 2H),

https://doi.org/10.1021/acsomega.1c03410
ACS Omega 2021, 6, 21169−21180

7.54 (d, J = 8.8 Hz, 1H), 7.51−7.39 (m, 3H), 7.34 (t, J = 7.2 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 196.9, 137.9, 136.2, 134.7, 134.5, 130.0, 129.2, 128.2, 127.9, 125.0, 124.3, 119.4, 55.6, 28.9. HR-MS (ESI-TOF) m/z: cal. for $C_{16}H_{12}BrClN_2S$ $[M + H]^+$: 378.9666 and 380.9668; found: 378.9681 and 380.9645.

*2-(2-Bromo-4-fluorophenyl)-2-cyano-N-phenylpropanethioamide (**3q**).* Yield: 72% (0.261 g); white solid; R_f: 0.30 in 30% EtOAc in hexanes; mp: 133−135 °C; IR (ν cm^{-1}) = 3427, 2359, 2236, 1656, 1530, 1222, 670; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.61−7.57 (m, 3H), 7.48−7.40 (m, 3H), 7.33 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 6.8 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 197.2, 162.5 (d, J = 253.4 Hz), 138.0, 132.0 (d, J = 3.5 Hz), 130.5 (d, J = 8.7 Hz), 129.2, 127.9, 125.1 (d, J = 9.4 Hz), 124.3, 122.5 (d, J = 24.7 Hz), 119.5, 115.1 (d, J = 21.0 Hz), 55.7, 29.0; ^{19}F NMR (376 Hz, $CDCl_3$) δ −109.71. HR-MS (ESI-TOF) m/z: cal. for $C_{16}H_{12}BrFN_2S$ $[M + H]^+$: 384.9781 and 386.9769; found: 384.9788 and 386.9760.

*2-(2-Bromo-3,5-di-tert-butylphenyl)-2-cyano-N-phenylpropanethioamide (**3r**).* Yield: 55% (0.251 g); pale yellow solid; R_f: 0.58 in 30% EtOAc in hexanes; mp: 178−180 °C; IR (ν cm^{-1}) = 3338, 3262, 2962, 2871, 2360, 2238, 1710, 1500, 1462, 1393, 1237, 1071, 885, 646, 488; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.65 (s, 1H), 7.56 (s, 1H), 7.48 (d, J = 7.7 Hz, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.30 (t, J = 7.7 Hz, 1H), 2.38 (s, 3H), 1.58 (s, 9H), 1.38 (s, 9H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 199.2, 150.4, 150.0, 138.2, 136.4, 129.1, 127.6, 127.1, 124.9, 124.4, 122.9, 120.5, 59.2, 38.1, 35.2, 31.2, 30.2, 29.9. HR-MS (ESI-TOF) m/z: cal. for $C_{24}H_{29}BrN_2S$ $[M + H]^+$: 457.1306 and 459.1286; found: 457.1308 and 459.1288.

*2-(2-Bromophenyl)-2-cyano-N-phenylpent-4-enethioamide (**3s**).* Yield: 60% (0.222 g); pale yellow solid; R_f: 0.5 in 30% EtOAc in hexanes; mp: 102−104 °C; IR (ν cm^{-1}) = 3841, 3004, 2347, 1697, 1558, 1541, 1269, 753, 664; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.62−7.53 (m, 4H), 7.37 (t, 3H), 7.28−7.19 (m, 2H), 2.81−2.73 (m, 1H), 2.61−2.53 (m, 1H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 137.9, 136.7, 136.2, 130.6, 129.7, 129.2, 127.9, 127.9, 124.4, 124.3, 118.7, 61.1, 33.8, 9.8. HR-MS (ESI-TOF) m/z: cal. for $C_{17}H_{16}BrN_2S$ $[M + H]^+$: 358.0139 and 360.0119; found: 358.0139 and 360.0139.

*2-(2-Bromophenyl)-2-cyano-N-3-diphenylpropanethioamide (**3t**).* Yield: 96% (0.404 g); yellow solid; R_f: 0.6 in 30% EtOAc in hexanes; mp: 150−152 °C; IR (ν cm^{-1}) = 3745, 3004, 2986, 2349, 1697, 1469, 1257, 763, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.65 (d, J = 8.0 Hz, 4H), 7.58 (d, J = 8.0 Hz, 3H), 7.40−7.36 (m, 3H), 7.31−7.24 (m, 6H), 7.21−7.17 (m, 1H), 7.08 (d, J = 7.6 Hz, 2H), 3.97 (d, J = 12.4 Hz, 1H), 3.72 (d, J = 12.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 137.6, 136.4, 136.2, 133.5, 130.65, 130.57, 129.4, 129.0, 128.6, 128.4, 127.9, 127.8, 124.8, 124.5, 118.6, 61.1, 44.9. HR-MS (ESI-TOF) m/z: cal. for $C_{22}H_{17}BrN_2S$ $[M + H]^+$: 443.0188 and 445.0168; found: 443.0183 and 445.0144.

*2-(2-Bromophenyl)-2-cyano-N-phenylpent-4-enethioamide (**3u**).* Yield: 74% (0.274 g); yellow solid; R_f: 0.32 in 30% EtOAc in hexanes; mp: 125−127 °C; IR (ν cm^{-1}) = 3343, 3274, 2359, 1595, 1467, 1374, 1076, 753, 641, 489; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.49−7.44 (m, 3H), 7.37−7.29 (m, 2H), 6.93−5.93 (m, 1H), 5.47−5.37 (m, 2H), 3.55 (dd, J = 13.0, 7.6 Hz, 1H), 3.36 (dd, J = 13.0, 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 137.9, 135.4, 135.2, 130.6, 130.1, 129.7, 129.2, 127.9, 127.9, 124.5, 124.4, 122.1, 118.5, 60.1, 44.3. HR-MS (ESI-TOF) m/z: cal. for $C_{17}H_{16}BrNO_2S$ $[M + H]^+$: 393.0032 and 395.0011; found: 393.0037 and 395.0023.

*Methyl 2-(2-bromophenyl)-2-methyl-3-(phenylamino)-3-thioxopropanoate (**3v**).* Yield: 70% (0.264 g); yellow solid; R_f: 0.32 in 30% EtOAc in hexanes; mp: 102−104 °C; IR (ν cm^{-1}) = 3189, 3061, 2949, 2359, 1717, 1497, 1255, 1032, 741, 557, 460; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.49 (s, 1H), 7.82 (d, J = 7.6 Hz, 2H), 7.65−7.54 (m, 2H), 7.51−7.40 (m, 3H), 7.31 (t, J = 7.6 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 3.78 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.39, 177.6, 141.8, 139.2, 133.4, 129.4, 128.9, 128.8, 127.2, 126.9, 125.2, 123.8, 63.1, 53.8, 29.0. HR-MS (ESI-TOF) m/z: cal. for $C_{17}H_{16}BrNO_2S$ $[M + H]^+$: 378.0158 and 380.0143; found: 378.0161 and 380.0138.

*2-(2-Bromophenyl)-2-cyano-N-(1-phenylethyl)-propanethioamide (**3w**).* Yield: 72% (0.268 g); yellow solid; R_f: 0.30 in 30% EtOAc in hexanes; mp: 132−134 °C; IR (ν cm^{-1}) = 3357, 3287, 3061, 2931, 2359, 2239, 1509, 1392, 1049, 995, 545; diastereoselectivity ratio: 1:1 (only one diastereomer is given); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.57 (t, J = 8.0 Hz, 2H), 7.49−7.38 (m, 5H), 5.77−5.74 (m, 1H), 2.26 (s, 3H), 1.68 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 140.6, 135.7, 135.2, 134.9, 130.7, 128.9, 128.1, 127.9, 126.4, 124.5, 119.6, 55.4, 55.5, 28.6, 19.3. HR-MS (ESI-TOF) m/z: cal. for $C_{18}H_{17}N_2SBr$ $[M + H]^+$: 373.0369 and 375.0348; found: 373.1061 and 375.0361.

*2-(2-Bromo-4,5-dimethoxyphenyl)-2-cyano-N-(1-phenylethyl)propanethioamide (**3x**).* Yield: 79% (0.342 g); pale yellow solid; R_f: 0.30 in 30% EtOAc in hexanes; mp: 94−96 °C; IR (ν cm^{-1}) = 3289, 2934, 2841, 2359, 1596, 1390, 1262, 1172, 1022, 855, 667; diastereoselectivity ratio: 1:1 (only one diastereomer is given); ^{1}H NMR (400 MHz) δ 7.93 (s, 1H), 7.39−7.35 (m, 5H), 7.095 (s, 1H), 7.03 (s, 1H), 5.75−5.71 (m, 1H), 3.879 (s, 6H), 2.21 (s, 3H), 1.64 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 150.1, 148.5, 140.3, 128.9, 128.2, 127.5, 126.8, 119.8, 117.6, 114.9, 112.3, 56.4, 55.54, 55.50, 55.1, 28.8, 19.4. HR-MS (ESI-TOF) m/z: cal. for $C_{20}H_{21}BrN_2O_2S$ $[M + H]^+$: 433.0580 and 435.0568; found: 433.0583 and 435.0560.

*2-(6-Bromo-3,4-methylenedioxyphenyl)-2-cyano-N-(1-phenylethyl)propanethioamide (**3y**).* Yield: 75% (0.312 g); yellow solid; R_f: 0.34 in 30% EtOAc in hexanes; mp: 142−144 °C; IR (ν cm^{-1}) = 3353, 2902, 2359, 1725, 1657, 1480, 1389, 1125, 699, 430; diastereoselectivity ratio: 1:1 (only one diastereomer is given); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.44−7.29 (m, 5H), 7.06 (s, 1H), 7.01 (s, 1H), 6.04 (s, 2H), 5.72−5.70 (m, 1H), 2.17 (s, 3H), 1.62 (d, J = 7.0 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 197.2, 149.0, 147.9, 140.2, 129.0, 128.9, 128.2, 119.6, 116.0, 114.7, 109.1, 102.5, 55.5, 55.4, 55.0, 29.3, 19.4. HR-MS (ESI-TOF) m/z: cal. for $C_{19}H_{17}BrN_2O_2S$ $[M + H]^+$: 417.0267 and 419.0247; found: 417.0266 and 419.0245.

*2-(2-Chlorophenyl)-2-cyano-N-phenylpropanethioamide (**3z**).* Yield: 74% (0.222 g); viscous liquid; R_f: 0.30 in 30% EtOAc in hexanes; IR (ν cm^{-1}) = 3230, 2996, 2984, 2290, 1734, 1479, 1235, 1018, 735, 565; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.36−7.33 (m, 4H), 7.24 (t, J = 8.0 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (100 MHz,

https://doi.org/10.1021/acsomega.1c03410
ACS Omega 2021, 6, 21169−21180

$CDCl_3$) δ 197.6, 138.0, 134.6, 134.4, 131.9, 130.9, 129.2, 128.9, 127.8, 127.6, 124.4, 119.8, 54.8, 28.2. HR-MS (ESI-TOF) *m/z*: cal. for $C_{16}H_{13}ClN_2S$ $[M + H]^+$: 301.0561; found: 301.0548.

*2-(2-Iodophenyl)-2-cyano-N-phenylpropanethioamide (**3aa**).* Yield: 70% (0.274 g); viscous liquid; R_f: 0.32 in 30% EtOAc in hexanes; IR (ν cm^{-1}) = 3234, 3012, 2997, 2306, 1729, 1468, 1249, 1006, 729, 640; ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.47−7.43 (m, 2H), 7.37−7.33 (m, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 142.7, 138.0, 130.9, 129.7, 129.4, 129.2, 128.9, 127.8, 124.3, 119.8, 99.2, 59.2, 29.4. HR-MS (ESI-TOF) *m/z*: cal. for $C_{16}H_{13}IN_2S$ $[M + H]^+$: 414.9736; found: 414.9743.

*Procedure for Optimization of Benzo[b]thiolane **1a**.* An oven-dried 8 mL reaction vial was charged with copper salt (5 mol %), base (1.5 mmol), the respective thioamide **3a** (0.5 mmol) in a solvent (2.0 mL). The mixture was stirred at 90 °C for 2.5−3.5 h. The reaction mixture was monitored by TLC. After the starting material was completely consumed, the reaction mixture was purified by flash chromatography using hexane and EtOAc as the eluents.

General Procedure for the Synthesis of Benzo[*b*]-thiolanes 1. An oven-dried 8 mL reaction vial was charged with CuBr (5 mol %), Et_3N (0.75 mmol), and respective thioamides **3a**−**y** in 2.0 mL of DMF solvent, which was stirred at 90 °C for 2.5−12 h. The reaction mixture was monitored by TLC. After the starting material was completely consumed, the reaction mixture was purified by flash chromatography using hexane and EtOAc as the eluents.

*3-Cyano-3-methyl-2-phenyliminobenzo[b]thiolane (**1a**).* Reaction time: 1.5 h; yield: 98% (0.129 g); pale yellow solid; R_f = 0.28 in 30% EtOAc in hexane; mp = 119−121 °C; IR (KBr, ν cm^{-1}): 3449, 2364, 1653, 1448, 1113, 667; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.2 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.36−7.30 (m, 2H), 7.26−7.21 (m, 2H), 7.05 (d, J = 8.0 Hz, 2H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 150.2, 135.7, 135.3, 130.3, 129.4, 126.9, 125.9, 124.6, 123.1, 119.7, 119.4, 52.0, 28.8. HR-MS (ESI-TOF), *m/z*: $[M + H]^+$ cal. for $C_{16}H_{12}N_2S$: 265.0794; found: 265.0799.

*3-Cyano-3-methyl-2-(4-methoxyphenyl)iminobenzo[b]-thiolane (**1b**).* Reaction time: 1.5 h; yield: 91% (0.134 g); pale yellow solid; R_f = 0.33 in 30% EtOAc in hexane; mp = 143−145 °C; IR (KBr, ν cm^{-1}): 2929, 2840, 2190, 1641, 1505, 1244, 838, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 8.0 Hz, 1H), 7.19−7.10 (m, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.8 Hz, 1H), 3.87 (s, 3H), 2.06 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 155.6, 145.3, 135.6, 134.2, 130.6, 127.5, 125.4, 124.8, 123.4, 120.2, 118.9, 52.3, 28.98, 28.99. HR-MS (ESI-TOF), *m/z*: [M + H] + cal. for $C_{17}H_{14}N_2OS$: 295.0900; found: 295.0908.

*3-Cyano-3-methyl-2-(4-methylphenyl)iminobenzo[b]-thiolane (**1c**).* Reaction time: 2 h; yield: 85% (0.129 g); brown viscous liquid; R_f = 0.29 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 2950, 2365, 1270, 1018, 759, 665; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.6 Hz, 1H), 7.38−7.29 (m, 2H), 7.26−7.23 (m, 3H), 6.99 (d, J = 8.0 Hz, 2H), 2.39 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 147.6, 135.72, 135.69, 135.4, 130.2, 129.9, 126.9, 124.6, 123.1, 119.8, 119.5, 52.0, 28.8, 21.1. HR-MS (ESI-TOF), *m/z*: $[M + Na]^+$ cal. for $C_{17}H_{14}N_2S$: 301.0770; found: 301.0787.

*3-Cyano-3-methyl-2-(4-fluorophenyl)iminobenzo[b]-thiolane (**1d**).* Reaction time: 1.5 h; yield: 79% (0.111 g); pale yellow solid; R_f = 0.28 in 30% EtOAc in hexane; mp = 148−150 °C; IR (KBr, ν cm^{-1}): 3335, 2150,1683, 1509, 1410, 1220, 838, 761; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71−7.65 (m, 2H), 7.49−7.46 (m, 1H), 7.42−7.39 (m, 2H), 7.35−7.30 (m, 1H), 7.05−7.00 (m, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 160.2 (d, J = 244.2 Hz), 135.2, 134.1, 132.7 (d, J = 2.9 Hz), 131.1, 129.2, 128.5, 123.8, 122.8 (d, J = 8.3 Hz), 119.4, 115.9 (d, J = 22.7 Hz), 50.1, 24.2; ^{19}F NMR (376 Hz, $CDCl_3$) δ −116.19. HR-MS (ESI-TOF), *m/z*: $[M + H]^+$ cal. for $C_{16}H_{11}N_2SF$: 283.0700; found: 283.0732.

*3-Cyano-3-methyl-2-(4-nitrophenyl)iminobenzo[b]-thiolane (**1e**).* Reaction time: 1 h; yield: 97% (0.149 g); pale yellow solid; R_f = 0.28 in 30% EtOAc in hexane; mp = 147−149 °C; IR (KBr, ν cm^{-1}): 3335, 2253, 1683, 1509, 1410, 1220, 838, 761; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 7.2 Hz, 1H), 7.42−7.38 (m, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 155.6, 145.3, 135.6, 134.1, 130.6, 127.5, 125.4, 124.8, 123.3, 120.2, 118.9, 52.3, 28.8. HR-MS (ESI-TOF), *m/z*: $[M + H]^+$ cal. for $C_{16}H_{11}N_3O_2S$: 310.0645; found: 310.0617.

*3-Cyano-3-methyl-2-(2-methoxyphenyl)iminobenzo[b]-thiolane (**1f**).* Reaction time: 1.5 h; yield: 90% (0.132 g); pale yellow solid; R_f = 0.32 in 30% EtOAc in hexane; mp = 106−108 °C; IR (KBr, ν cm^{-1}): 3469, 2837, 2240, 1651, 1589, 1490, 1254, 751, 712; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.2 Hz, 1H), 7.36−7.26 (m, 2H), 7.23−7.17 (m, 2H), 7.01−6.96 (m, 2H), 6.92 (d, J = 7.6 Hz, 1H), 3.83 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 149.6, 139.6, 136.0, 135.4, 130.2, 126.8, 126.7, 124.6, 123.0, 121.1, 119.8, 119.3, 112.3, 112.3, 55.9, 51.6, 28.8. HR-MS (ESI-TOF), *m/z*: $[M + H]^+$ cal. for $C_{17}H_{14}N_2OS$: 295.0900; found: 295.0914.

*3-Cyano-3-methyl-2-(2-trifluoromethylphenyl)-iminobenzo[b]thiolane (**1g**).* Reaction time: 2.5 h; yield: 75% (0.124 g); pale yellow solid; R_f = 0.25 in 30% EtOAc in hexane; mp = 106−108 °C; IR (KBr, ν cm^{-1}): 3851, 2949, 2258, 1700, 1507, 1289, 665; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 1H), 7.62−7.56 (m, 2H), 7.39−7.30 (m, 3H), 7.26 (d, J = 7.6 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 148.56, 148.55, 135.8, 134.6, 133.1, 130.5, 127.2, 126.8 (q, J = 9.5 Hz), 125.3, 124.8, 123.5 (q, J = 271.6 Hz), 120.8 (q, J = 30.8 Hz), 119.2, 118.9, 51.9, 28.4; ^{19}F NMR (376 Hz, $CDCl_3$) δ −61.44. HR-MS (ESI-TOF), *m/z*: $[M + H]^+$ cal. for $C_{17}H_{11}F_3N_2S$: 333.0668; found: 333.0666.

*3-Cyano-3-methyl-2-(benzyl)iminobenzo[b]thiolane (**1h**).* Reaction time: 6 h; yield: 65% (0.090 g); pale yellow solid; R_f = 0.28 in 30% EtOAc in hexane; mp = 84−86 °C; IR (KBr, ν cm^{-1}): 3449, 2364, 1653, 1490, 1254, 751, 667; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.2 Hz, 1H), 7.43−7.28 (m, 8H), 4.71 (d, J = 15.6 Hz, 1H), 4.56 (d, J = 15.6 Hz, 1H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 137.9, 136.0, 134.8, 130.2, 128.5, 127.6, 127.2, 126.9, 124.6, 123.2, 119.7, 61.1, 51.6, 28.8. HR-MS (ESI-TOF), *m/z*: $[M + H]^+$ cal. for $C_{17}H_{14}N_2S$: 279.0950; found: 279.0958.

*3-Cyano-3-methyl-2-(isopropyl)iminobenzo[b]thiolane (**1i**).* Reaction time: 6 h; yield: 73% (0.084 g); brown viscous liquid; R_f = 0.28 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 3547, 2934, 2238, 1651, 1130, 987, 756; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.2 Hz, 1H), 7.38−7.27 (m, 3H), 3.40−

https://doi.org/10.1021/acsomega.1c03410
ACS Omega 2021, 6, 21169−21180

3.34 (m, 1H), 1.90 (s, 3H), 1.31 (d, J = 6.0 Hz, 3H), 1.25 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 135.9, 135.2, 130.0, 126.6, 124.5, 123.1, 119.9, 59.7, 51.2, 28.8, 22.5, 22.4. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{13}H_{14}N_2S$: 231.0950; found: 231.0944.

3-Cyano-3-methyl-2-(ethyl)iminobenzo[b]thiolane (**1j**). Reaction time: 12 h; yield: 79% (0.084 g); yellow viscous liquid; R_f = 0.28 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 3452, 2979, 2349, 1656, 1470, 982, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.0 Hz, 1H), 7.38−7.28 (m, 3H), 3.52−3.34 (m, 2H), 1.91 (s, 3H), 1.36 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 136.0, 135.0, 130.1, 126.7, 124.5, 123.2, 119.8, 52.8, 51.3, 28.8, 14.7. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{12}H_{12}N_2S$: 217.0794; found: 217.0805.

3-Cyano-3-methyl-2-(tert-butyl)iminobenzo[b]thiolane (**1k**). Reaction time: 6.5 h; yield: 77% (0.094 g); yellow viscous liquid; R_f = 0.28 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 3452, 2979, 2336, 1656, 1512, 1470, 982, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.2 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.34−7.24 (m, 2H), 1.86 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 136.7, 135.3, 129.9, 126.4, 124.4, 122.6, 120.3, 57.2, 53.6, 29.3, 28.1. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{14}H_{16}N_2S$: 245.1107; found: 245.1109.

3-Cyano-3-methyl-2-phenylimino-5,6-dimethoxybenzo-[b]thiolane (**1l**). Reaction time: 1 h; yield: 96% (0.155 g); brown viscous liquid; R_f = 0.28 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 2946, 2365, 2237, 1265, 1012, 810, 657; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 7.46 (t, J = 7.6 Hz, 2H), 7.39 (s, 1H), 7.25 (t, J = 7.0 Hz, 2H), 7.14 (s, 1H), 7.04 (d, J = 8.0 Hz, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 169.1, 151.4, 150.5, 149.2, 130.0, 126.8, 126.2, 125.4, 120.2, 119.8, 109.2, 107.4, 56.7, 56.5, 52.2, 27.9. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{18}H_{16}N_2O_2S$: 325.1005; found: 325.1032.

3-Cyano-3-methyl-2-(phenylimino)-5,6-methylenedioxybenzo[b]thiolane (**1m**). Reaction time: 1 h; yield: 92% (0.155 g); pale yellow solid; mp = 121−123 °C; R_f = 0.28 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 2952, 2815, 2340, 1628, 1539, 1195, 750, 660; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, J = 7.8 Hz, 2H), 7.24 (t, J = 7.0 Hz, 1H), 7.05 (d, J = 8.0 Hz, 2H), 6.69 (s, 1H), 6.03 (s, 2H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 150.1, 149.5, 147.5, 129.4, 127.7, 126.9, 125.9, 119.7, 119.4, 105.2, 103.6, 102.0, 52.1, 28.7. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{17}H_{12}N_2O_2S$: 309.0692; found: 309.0631.

3-Cyano-3-methyl-2-phenylimino-6,7-dimethoxybenzo-[b]thiolane (**1n**). Reaction time: 2 h; yield: 79% (0.128 g); white solid; mp = 128−130 °C; R_f = 0.30 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 2930, 2829, 2339, 1630, 1506, 1239, 826, 700; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40 (t, J = 7.7 Hz, 2H), 7.20 (t, J = 7.7 Hz, 1H), 7.03 (d, J = 7.7 Hz, 2H), 6.92 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 4.10 (s, 3H), 3.88 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.0, 151.5, 150.4, 146.7, 129.3, 129.0, 126.3, 125.7, 119.6, 117.6, 114.7, 60.9, 56.2, 51.2, 26.6. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{18}H_{16}N_2O_2S$: 325.1005; found: 325.1004.

3-Cyano-3-methyl-2-(4-methylphenyl)imino-6,7-dimethoxybenzo[b]thiolane (**1o**). Reaction time: 2 h; yield: 80% (0.135 g); pale yellow solid; mp = 124−126 °C; R_f = 0.28 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 2949, 2367, 1269, 1016, 811, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.0 Hz, 2H), 6.96−6.85 (m, 4H), 4.09 (s, 3H), 3.88 (s, 3H), 2.36 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 167.1, 151.4, 147.8, 146.7, 135.4, 129.8, 129.0, 126.5, 119.7, 119.6, 117.5, 114.6, 60.8, 56.2, 51.2, 26.6, 21.0. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{19}H_{18}N_2O_2S$: 339.1162; found: 339.1161.

3-Cyano-3-methyl-2-phenylimino-6-chlorobenzo[b]-thiolane (**1p**). Reaction time: 1 h; yield: 42% (0.062 g); brown viscous liquid; R_f = 0.28 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 3442, 2362, 1641, 1252, 970, 670; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.43 (m, 3H), 7.32−7.24 (m, 3H), 7.06 (d, J = 7.6 Hz, 2H), 2.05(s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 165.6, 149.8, 137.2, 136.2, 129.5, 127.3, 126.1, 125.5, 123.1, 119.6, 118.9, 51.5, 28.7. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{16}H_{11}ClN_2S$: 299.0404; found: 299.0393.

3-Cyano-3-methyl-2-phenylimino-6-fluorobenzo[b]-thiolane (**1q**). Reaction time: 1 h; yield: 35% (0.049 g); white solid; mp = 106−108 °C; R_f = 0.28 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 3427, 2359, 1656, 1222, 670; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.48 (m, 1H), 7.43−7.39 (m, 2H), 7.25−7.21 (m, 1H), 7.04−7.00 (m, 3H), 6.99−6.95 (m, 1H), 2.02 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 165.4 (d, J = 234 Hz), 162.3, 149.9, 137.4 (d, J = 16.9 Hz), 131.5 (d, J = 8.0 Hz), 129.5, 126.2, 126.0 (d, J = 16.1 Hz), 119.7, 119.2, 114.3 (d, J = 40 Hz), 110.8 (d, J = 45.1 Hz), 51.3, 28.9; ^{19}F NMR (376 Hz, $CDCl_3$) δ −109.43. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{16}H_{11}FN_2S$: 283.0700; found: 283.0678.

3-Cyano-3-methyl-2-phenylimino-4,6-di-tertbutylbenzo-[b]thiolane (**1r**). Reaction time: 3 h; yield: 92%; pale yellow solid; mp = 192−194 °C; R_f = 0.28 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 2964, 2341, 1635, 1538, 1436, 1145, 1071, 743, 502, 442; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.44−7.42 (m, 4H), 7.22 (t, J = 7.7 Hz, 1H), 7.08 (d, J = 7.7 Hz, 2H), 2.04 (s, 3H), 1.36 (s, 9H), 1.35(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 150.4, 144.9, 136.7, 129.3, 129.2, 125.6, 124.7, 120.0, 119.9, 119.2, 51.7, 35.8, 34.9, 31.3, 29.4, 29.3. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{24}H_{28}N_2S$: 377.2046; found: 377.2050.

3-Cyano-3-ethyl-2-phenyliminobenzo[b]thiolane (**1s**). Reaction time: 2.5 h; yield: 95%; pale yellow solid; R_f: 0.6 in 30% EtOAc in hexane; mp = 85−86 °C; IR (KBr, ν cm^{-1}) = 3738, 3006, 2989, 2849, 2253, 1763, 1279, 1264, 763, 656. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.48 (m, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.37−7.28 (m, 2H), 7.24−7.19 (m, 2H), 7.04−7.01 (m, 2H), 2.51−2.41 (m, 1H), 2.39−2.32 (m, 1H), 1.05 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 150.4, 136.4, 134.2, 130.2, 129.5, 126.8, 125.9, 125.0, 123.1, 119.7, 119.0, 56.6, 35.9, 8.1. HR-MS (ESI-TOF), m/z $[M + H]^+$ cal. for $C_{17}H_{14}N_2S$: 279.0950; found: 279.0954.

3-Cyano-3-benzyl-2-phenyliminobenzo[b]thiolane (**1t**). Reaction time: 2.5 h; yield: 85%; white solid; R_f: 0.7 in 30% EtOAc in hexanes; mp = 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J = 7.6 Hz, 2H), 7.25−7.14 (m, 7H), 7.04 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 7.6 Hz, 2H), 6.89 (d, J = 6.8 Hz, 2H), 3.60−3.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 150.1, 136.5, 133.3, 132.5, 130.7, 130.3, 129.4, 128.2, 128.0, 126.3, 125.95, 125.86, 122.9, 119.8, 118.5, 57.1, 48.0. HR-MS (ESI-TOF), m/z $[M + H]^+$ cal. for $C_{22}H_{16}N_2S$: 341.1107; found: 341.1092.

3-Cyano-3-allyl-2-phenyliminobenzo[b]thiolane (**1u**). Reaction time: 6 h; yield: 52% (0.075 g); viscous liquid; R_f = 0.28 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 3447, 2956, 2248, 1652, 1465, 960, 742, 656; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 4H), 7.44 (t, J = 7.8 Hz, 2H), 7.39−7.31 (m, 2H), 7.25 (d, J = 7.2 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H),

https://doi.org/10.1021/acsomega.1c03410
ACS Omega 2021, 6, 21169−21180

5.81−5.70 (m, 1H), 5.24 (t, J = 15.2 Hz, 2H), 3.13 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 150.3, 136.1, 133.7, 130.2, 129.4, 129.1, 126.6, 125.9, 125.3, 123.0, 121.9, 119.7, 118.5, 55.7, 46.3. HR-MS (ESI-TOF), m/z: $[M + Na]^+$ cal. for $C_{18}H_{14}N_2S$: 313.0770; found: 313.0803.

*3-Methyl ester-3-methyl-2-phenyliminobenzo[b]thiolane (**1v**).* Reaction time: 3.5 h; yield: 89% (0.132 g); brown viscous compound; R_f = 0.28 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 2954, 2280, 1745, 1487, 1237, 959, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.6 Hz, 1H), 7.37−7.27 (m, 4H), 7.08 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.04(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 157.8, 142.9, 136.6, 135.5, 130.2, 126.9, 124.6, 123.1, 121.6, 119.6, 144.5, 55.5, 52.2, 28.9. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{17}H_{15}N_2OS$: 298.0896; found: 298.0905.

*3-Cyano-3-methyl-2-(1-phenylethyl)iminobenzo[b]-thiolane (**1w**).* Reaction time: 1.5 h; yield: 75% (0.109 g); viscous liquid; R_f = 0.29 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 3061, 2972, 2850, 2240, 1651, 1352, 1026, 884, 578; diastereoselectivity ratio: 1:1 (only one diastereomer is given); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.45 (m, 3H), 7.41−7.35 (m, 3H), 7.32−7.28 (m, 3H), 4.44−4.38 (m, 1H), 2.00 (s, 3H), 1.66 (d, J = 6.4 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 162.8, 143.7, 135.9, 135.1, 130.1, 128.5, 127.2, 126.8, 126.4, 124.6, 123.2, 119.7, 66.9, 51.5, 29.1, 23.9. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{18}H_{16}N_2S$: 293.1107; found: 293.1135.

*3-Cyano-3-methyl-2-(1-phenylethyl)imino-5,6-methylenedioxybenzo[b]thiolane (**1x**).* Reaction time: 2 h; yield: 75% (0.132 g); viscous liquid; R_f = 0.32 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 2967, 2359, 1653, 1497, 1277, 1175, 1032, 699, 435; diastereoselectivity ratio: 1:1 (only one diastereomer is given); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.28 (m, 5H), 6.99 (s, 1H), 6.76 (s, 1H), 4.36−4.33 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 1.96 (s, 3H), 1.62 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 150.9, 149.6, 143.7, 128.5, 127.2, 125.9, 120.1, 114.0, 107.5, 105.9, 67.3, 56.3, 51.9, 29.7, 29.0, 23.9. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{20}H_{20}N_2O_2S$: 353.1318; found: 353.1301.

*3-Cyano-3-methyl-2-(1-phenylethyl)imino-5,6-dimethoxybenzo[b]thiolane (**1y**).* Reaction time: 2.5 h; yield: 66% (0.126 g); viscous liquid; R_f = 0.30 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 2958, 2365, 1637, 1285, 1167, 1022, 720, 585; diastereoselectivity ratio: 1:1 (only one diastereomer is given); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.28 (m, 5H), 6.79 (s, 1H), 6.74 (s, 1H), 6.01 (s, 2H), 4.36−4.33 (m, 1H), 1.95 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 142.7, 136.6, 132.9, 132.4, 128.59, 128.58, 127.9, 127.7, 126.7, 126.2, 114.0, 113.9, 50.2, 50.1, 40.1, 34.2. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{19}H_{16}N_2O_2S$: 337.1005; found: 337.1000.

*Procedure for (Z)-3-Methyl-2-(phenylimino)-2,3-dihydrobenzo[b]thiophene-3-carboxamide (**7a**).* An oven-dried 8 mL reaction vial was charged with **1a** (0.50 mmol) and TfOH (5 mmol) in 2.0 mL of DCE solvent, which was stirred at 60 °C for 2 h. The reaction mixture was monitored by TLC. After the starting material was completely consumed, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was washed with water (3 × 25 mL), dried over anhydrous Na_2SO_4, and concentrated under a reduced pressure. The crude product was purified by flash chromatography using hexane and EtOAc as the eluents.

Reaction time: 2 h; yield: 77% (0.108 g); pale yellow solid; R_f = 0.28 in 30% EtOAc in hexane; mp = 121−123 °C; IR (KBr, ν cm^{-1}): 2958, 2365, 1637, 1285, 1167, 1022, 720, 585; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.31 (m, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.30−7.24 (m, 4H), 7.04 (d, J = 7.2 Hz, 2H), 5.64 (s, 1H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 172.3, 151.2, 139.4, 135.0, 129.5, 129.0, 127.0, 126.2, 125.6, 122.3, 119.8, 63.5, 28.4. HR-MS (ESI-TOF), m/z: $[M + Na]^+$ cal. for $C_{16}H_{14}N_2OS$: 305.0719; found: 305.0725.

*Procedure for 2-(2-Mercaptophenyl)-2-methyl-N-phenyl-malonamide (**8a**).* In an oven-dried round-bottom flask, **1a** (0.5 mmol) was taken. To it, conc. H_2SO_4 was added (10 mL). Then, it was stirred at room temperature for 2 h (in the case of HCl, **1a** was dissolved in EtOH (12 mL). To it, conc. HCl (1.5 mmol) was added. Then, it was stirred at 60 °C for 3 h). After the starting material (monitored by TLC) was completely consumed, the reaction was quenched with cold $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was washed with water (3 × 25 mL), dried over anhydrous Na_2SO_4, and concentrated under a reduced pressure. The crude product was purified by flash chromatography using hexane and EtOAc as eluents.

Reaction time: 2 h; yield: 99% (0.148 g) [68% (0.102 g)]; viscous liquid; R_f = 0.25 in 30% EtOAc in hexane; IR (KBr, ν cm^{-1}): 2960, 2100, 1549, 1290, 1158, 1122, 720, 585; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.65 (m, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.32−7.23 (m, 4H), 7.06 (d, J = 7.2 Hz, 2H), 5.83 (s, 1H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 172.0, 151.0, 139.2, 134.9, 129.4, 128.9, 126.9, 126.1, 125.5, 122.2, 119.7, 63.4, 28. HR-MS (ESI-TOF), m/z: $[M + H]^+$ cal. for $C_{16}H_{16}N_2O_2S$: 301.1000; found: 301.1010.

Crystal data for **1a** in CH_2Cl_2/n-hexane: $C_{16}H_{12}N_2S$, M_w = 264.34, triclinic, space group P-1, a = 8.1526(2) Å, b = 9.0963(2) Å, c = 10.4069(2) Å, α = 106.308(2)°, β = 104.374(2)°, γ = 103.637(2)°, V = 677.69(3) Å^3, Z = 2, D_{calc} = 1.295 g/cm^3, T = 291 K, $R1$ = 0.0408(2645), w$R2$ = 0.1105(2813), and GOF = 1.046.

Crystal data for **7a** in CH_2Cl_2/n-hexane: $C_{16}H_{14}N_2OS$, M_w = 282.35, monoclinic, space group C 2/c, a = 18.6061(13) Å, b = 6.3779(3) Å, c = 24.5520(12) Å, α = 90°, β = 103.547(4)°, γ = 90°, V = 2832.5(3) Å^3, Z = 8, D_{calc} = 1.324 g/cm^3, T = 293 K, $R1$ = 0.0149(2945), w$R2$ = 0.0276(3228), and GOF = 1.092.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c03410.

^{1}H NMR and ^{13}C NMR spectra of all of the compounds, synthesis of α-trisubstituted thioamides, and HPLC data of **1w−y** and **3w−y** (PDF)

X-ray crystallographic data for compounds **4a** and **7a** (CIF)

X-ray data were also deposited at the CCDC (entries 2082713 and 2082714) (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Saravanan Peruncheralathan − *School of Chemical Sciences, National Institute of Science Education and Research (NISER), Khurda 752050 Odisha, India;* orcid.org/0000-0003-2743-2447; Email: peru@niser.ac.in

https://doi.org/10.1021/acsomega.1c03410
ACS Omega 2021, 6, 21169−21180

Authors

Anwesha Bhattacharya − *School of Chemical Sciences, National Institute of Science Education and Research (NISER), Khurda 752050 Odisha, India*

Annaram Thirupathi − *School of Chemical Sciences, National Institute of Science Education and Research (NISER), Khurda 752050 Odisha, India*

Pradeep Natarajan − *School of Chemical Sciences, National Institute of Science Education and Research (NISER), Khurda 752050 Odisha, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c03410

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Department of Atomic Energy supported this work. We thank the Science and Engineering Research Board (SERB), New Delhi (Grant EMR/2017/005521) for the financial support. We thank Dr. Krishnan Venkatasubbaiah for solving one of the X-ray crystal data.

■ REFERENCES

(1) Selected papers (a) Lu, Y.; Gutgesell, M. L.; Xiong, R.; Zhao, J.; Li, Y.; Rosales, I. C.; Hollas, M.; Shen, Z.; Gordon-Blake, J.; Dye, K.; Wang, Y.; Lee, S.; Chen, H.; He, D.; Dubrovyskyii, O.; Zhao, H.; Huang, F.; Lasek, W. A.; Tonetti, A. D.; Thatcher, R. J. G. Design and Synthesis of Basic Selective Estrogen Receptor Degraders for Endocrine Therapy Resistant Breast Cancer. *J. Med. Chem.* **2019**, *62*, 11301−11323. (b) Kawamoto, Y.; Tomino, M.; Hiramatsu, K.; Oyama, Y.; Hayashi, Y. Benzothiophene derivatives as phosphodiesterase 10A (PDE10A) inhibitors: Hit-to-lead studies. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1419−1422. (c) Pieroni, M.; Azzali, E.; Basilico, N.; Parapini, S.; Zolkiewski, M.; Beato, C.; Annunziato, G.; Bruno, A.; Vacondio, F.; Costantino, G. Accepting the Invitation to Open Innovation in Malaria Drug Discovery: Synthesis, Biological Evaluation, and Investigation on the Structure−Activity Relationships of Benzo[*b*]thiophene-2-carboxamides as Antimalarial Agents. *J. Med. Chem.* **2017**, *60*, 1959−1970. (d) Chalmers, J. M.; Wang, Y.; Novick, S.; Sato, M.; Bryant, U. H.; Montrose-Rafizdeh, C.; Griffin, R. P.; Dodge, A. J. Hydrophobic Interactions Improve Selectivity to ERα for Benzothiophene SERMs. *ACS Med. Chem. Lett.* **2012**, *3*, 207−210. (e) Berrade, L.; Aisa, B.; Ramirez, J. M.; Galiano, S.; Guccione, S.; Moltzau, R. L.; Levy, O. F.; Nicoletti, F.; Battaglia, G.; Molinaro, G.; Aldana, I.; Monge, A.; Perez-Silanes, S. Novel Benzo[*b*]thiophene Derivatives as New Potential Antidepressants with Rapid Onset of Action. *J. Med. Chem.* **2011**, *54*, 3086−3090. (f) Qin, Z.; Kastrati, I.; Chandrasena, R. E. P.; Liu, H.; Yao, P.; Petukhov, P. A.; Bolton, J. L.; Thatcher, G. R. J. Benzothiophene Selective Estrogen Receptor Modulators with Modulated Oxidative Activity and Receptor Affinity. *J. Med. Chem.* **2007**, *50*, 2682−2692.

(2) Mitsui, C.; Okamoto, T.; Yamagishi, M.; Tsurumi, J.; Yoshimoto, K.; Nakahara, K.; Soeda, J.; Hirose, Y.; Sato, H.; Yamano, A.; Uemura, T.; Takeya, J. High-Performance Solution-Processable N-Shaped Organic Semiconducting Materials with Stabilized Crystal Phase. *Adv. Mater.* **2014**, *26*, 4546−4551.

(3) Selected Benzothiophene synthesis (a) Zhang, D.; Cai, J.; Du, J.; Wang, X.; He, W.; Yang, Z.; Liu, C.; Fang, Z.; Guo, K. Oxidant- and Catalyst-Free Synthesis of Sulfonated Benzothiophenes via Electrooxidative Tandem Cyclization. *J. Org. Chem.* **2021**, *86*, 2593−2601. (b) Matsuzawa, T.; Hosoya, T.; Yoshida, S. Transition-Metal-Free Synthesis of *N*-Arylphenothiazines through an *N*- and *S*-Arylation Sequence. *Org. Lett.* **2021**, *23*, 2347−2352. (c) Wang, H.; Wu, Q.; Zhang, J. D.; Li, H. Y.; Li, H. X. Photocatalyst- and Transition-Metal-Free Visible-Light-Promoted Intramolecular C(sp^2)−S Formation. *Org. Lett.* **2021**, *23*, 2078−2083. (d) Sundaravelu, N.; Nandy, A.; Sekar, G. Visible Light Mediated Photocatalyst Free C−S Cross Coupling: Domino Synthesis of Thiochromane Derivatives via Photoinduced Electron Transfer. *Org. Lett.* **2021**, *23*, 3115−3119. (e) Kumar, Y.; Ila, H. Synthesis of Substituted Benzo[*b*]thiophenes via Base-Promoted Domino Condensation−Intramolecular C−S Bond Formation. *Org. Lett.* **2021**, *23*, 1698−1702. (f) Cai, T.; Shen, F.; Ni, Y.; Xu, H.; Shen, R.; Gao, Y. Cascade Radical Annulation of 2-Alkynylthio(seleno)anisoles with Acetone or Acetonitrile: Synthesis of 3-Acetonethyl- or Cyanomethyl-Substituted Benzothio-(seleno)phenes. *J. Org. Chem.* **2021**, *86*, 1002−1011. (g) Zhang, W.; Tao, S.; Ge, H.; Li, Q.; Ai, Z.; Li, X.; Zhang, B.; Sun, F.; Xu, X.; Du, Y. Construction of 2-Arylbenzo[4,5]thieno[2,3-*d*]thiazole Skeleton via CuCl/S-Mediated Three-Component Reaction. *Org. Lett.* **2020**, *22*, 448−452. (h) Cheng, B.; Li, Y.; Wang, T.; Zhang, X.; Li, H.; He, Y.; Li, Y.; Zhai, H. Application of Pyridinium 1,4-Zwitterionic Thiolates: Synthesis of Benzopyridothiazepines and Benzothiophenes. *J. Org. Chem.* **2020**, *85*, 6794−6802. (i) Matsuzawa, T.; Hosoya, T.; Yoshida, S. One-step synthesis of benzo[*b*]thiophenes by aryne reaction with alkynyl sulfides. *Chem. Sci.* **2020**, *11*, 9691−9696. (j) Zhang, J.; Zhuang, Y.; Ma, Y.; Yang, X.; Szostak, M. Palladium-Catalyzed Synthesis of Benzothiophenes via Cross-Dehydrogenative Coupling of 4-Arylthiocoumarins and Pyrones. *Adv. Synth. Catal.* **2019**, *361*, 5709−5714. (k) Xu, D.; Qi, X.; Duan, M.; Yu, Z.; Zhu, L.; Shan, C.; Yue, X.; Bai, R.; Lan, Y. Thiolate−palladium(IV) or sulfonium−palladate(0)? A theoretical study on the mechanism of palladium-catalyzed C−S bond formation reactions. *Org. Chem. Front.* **2017**, *4*, 943−950. (l) Xie, X.; Li, P.; Shi, Q.; Wang, L. Visible-light-induced tandem cyclization of 2-alkynylanilines with disulfides: a convenient method for accessing benzothiophenes under transition-metal-free and photocatalyst-free conditions. *Org. Biomol. Chem.* **2017**, *15*, 7678−7684. (m) Masuya, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2016**, *18*, 4312−4315. (n) Tandem Thien- and Benzannulations of α-Alkenoyl-α-alkynyl Ketene Dithioacetals with Cyanoacetates: Synthesis of Functionalized Benzo[*b*]thiophenes. *Org. Lett.* **2015**, *17*, 1746−1749. Selected Review (o) Sundaravelu, N.; Sangeetha, S.; Sekar, G. Metal-catalyzed C−S bond formation using sulfur surrogates. *Org. Biomol. Chem.* **2021**, *19*, 1459−1459.

(4) (a) Godoi, B.; Schumacher, R. F.; Zeni, G. Synthesis of Heterocycles via Electrophilic Cyclization of Alkynes Containing Heteroatom. *Chem. Rev.* **2011**, *111*, 2937−2980. (b) Takimiya, K.; Osaka, I.; Mori, T.; Nakano, M. Organic Semiconductors Based on [1]Benzothieno[3,2-*b*][1]benzothiophene Substructure. *Acc. Chem. Res.* **2014**, *47*, 1493−1502. (c) Yao, H.; Ye, L.; Zhang, H.; Li, S.; Zhang, S.; Hou, J. Molecular Design of Benzodithiophene-Based Organic Photovoltaic Materials. *Chem. Rev.* **2016**, *116*, 7397−7457. (d) Wu, B.; Yoshikai, N. Recent developments in synthetic methods for benzo[*b*]heteroles. *Org. Biomol. Chem.* **2016**, *14*, 5402−5416.

(5) (a) Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Cara, C. L.; Preti, D.; Fruttarolo, F.; Pavani, M. G.; Tabrizi, M. A.; Tolomeo, M.; Grimaudo, S.; di Cristina, A.; Balzarini, J.; Hadfield, J. A.; Brancale, A.; Hamel, E. Synthesis and Biological Evaluation of 2- and 3-Aminobenzo[*b*]thiophene Derivatives as Antimitotic Agents and Inhibitors of Tubulin Polymerization. *J. Med. Chem.* **2007**, *50*, 2273−2277. (b) Chonan, T.; Wakasugi, D.; Yamamoto, D.; Yashiro, M.; Oi, T.; Tanaka, H.; Ohoka-Sugita, A.; Io, F.; Koretsune, H.; Hiratate, A. Discovery of novel (4-piperidinyl)-piperazines as potent and orally active acetyl-CoA carboxylase 1/2 non-selective inhibitors: F-Boc and triF-Boc groups are acid-stable bioisosteres for the Boc group. *Bioorg. Med. Chem.* **2011**, *19*, 1580−1593.

(6) Dadiboyena, S. Recent advances in the synthesis of raloxifene: A selective estrogen receptor modulator. *Eur. J. Med. Chem.* **2012**, *51*, 17−34.

(7) Selected 2-Aminobenzothiophene synthesis: (a) Stacy, G. W.; Villaescusa, F. W.; Wollner, T. E. 2-Aminobenzo[*b*]thiophene. An Aromatic Ring Tautomer1,2. *J. Org. Chem.* **1965**, *30*, 4074−4078. (b) Grandclaudon, P.; Lablache-Combier, A. Addition of Cyclic Secondary Amines to Benzo[*b*]thiophene and 3-Methylbenzo[*b*]-thiophene. *J. Org. Chem.* **1978**, *43*, 4379−4381. (c) Solovyev, A. Y.;

Androsov, D. A.; Neckers, D. C. One-Pot Synthesis of Substituted 2-Aminobenzo[*b*]thiophenes. *J. Org. Chem.* **2007**, *72*, 3122−3124. (d) Singh, P. P.; Yadav, A. K.; Ila, H.; Junjappa, H. Novel Route to 2,3-Substituted Benzo[*b*]thiophenes via Intramolecular Radical Cyclization. *J. Org. Chem.* **2009**, *74*, 5496−5501. (e) Androsov, D. A.; Solovyev, A. Y.; Petrov, M. L.; Butcher, R. J.; Jasinski, J. P. A convenient approach towards 2- and 3-aminobenzo[*b*]thiophenes. *Tetrahedron* **2010**, *66*, 2474−2485. (f) Hou, C.; He, Q.; Yang, C. Direct Synthesis of Diverse 2-Aminobenzo[*b*]thiophenes via Palladium-Catalyzed Carbon−Sulfur Bond Formation Using $Na_2S_2O_3$ as the Sulfur Source. *Org. Lett.* **2014**, *16*, 5040−5043. (g) Adib, M.; Soheilizad, M.; Rajai-daryasaraei, S.; Mirzaei, P. An Efficient Aromatization of 2-Amino-4,5,6,7-tetrahydrobenzo-[*b*]thiophene-3-carboxylates in Dimethyl Sulfoxide Catalyzed by *p*-Toluenesulfonic Acid. *Synlett* **2015**, *26*, 1101−1105. (h) Krishnananthan, S.; Smith, D.; Traeger, S. C.; Mathur, A.; Li, J. An efficient one-pot synthesis of substituted 2-aminobenzo-1-thiophene-3-carbonitriles. *Tetrahedron Lett.* **2015**, *56*, 3766−3768.

(8) Two compounds are reported (a) Soria-Castro, S. M.; Bisogno, F. R.; Peñéñory, A. B. Versatile one-pot synthesis of benzo-fused thiacycles by copper catalysis. *Org. Chem. Front.* **2017**, *4*, 1533−1540. (b) Nandi, C. G.; Singh, S. M. *p*-TSA/Base-Promoted Propargylation/Cyclization of *ß*-Ketothioamides for the Regioselective Synthesis of Highly Substituted (Hydro)thiophenes. *J. Org. Chem.* **2016**, *81*, 5824−5836.

(9) Selected synthesis of 2-Iminothiolanes (a) Wang, H.; Yang, W.; Liu, H.; Wang, W.; Li, H. $FeCl_3$ promoted highly regioselective [3 + 2] cycloaddition of dimethyl 2-vinyl and aryl cyclopropane-1,1-dicarboxylates with aryl isothiocyanates. *Org. Biomol. Chem.* **2012**, *10*, 5032−5035. (b) Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A.; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314−5317. (c) Tsunoi, S.; Maruoka, Y.; Suzuki, I.; Shibata, I. Catalytic [3 + 2] Cycloaddition through Ring Cleavage of Simple Cyclopropanes with Isocyanates. *Org. Lett.* **2015**, *17*, 4010−4013. (d) Huang, X.-Y.; Ding, R.; Mo, Z.-Y.; Xu, Y.-L.; Tang, H.-T.; Wang, H.-S.; Chen, Y.-Y.; Pan, Y.-M. Photocatalytic Construction of S−S and C−S Bonds Promoted by Acridinium Salt: An Unexpected Pathway To Synthesize 1,2,4-Dithiazoles. *Org. Lett.* **2018**, *20*, 4819−4823. (e) Kreft, A.; Jones, P. G.; Werz, D. B. The Cyclopropyl Group as a Neglected Donor in Donor−Acceptor Cyclopropane Chemistry. *Org. Lett.* **2018**, *20*, 2059−2062.

(10) Witalewska, M.; Wrona-Piotrowicz, A.; Makal, A.; Zakrzewski, J. Polycyclic Aromatic *N*-Ethoxycarbonyl Thioamide *S*-Oxides and Their Triflic Acid Promoted Cyclization to Fluorescent Thiophene Imine-Fused Arenes. *J. Org. Chem.* **2018**, *83*, 1933−1939.

(11) (a) Kita, Y.; Egi, M.; Ohtsubo, M.; Saiki, T.; Takada, T.; Tohma, H. Novel and efficient synthesis of sulfur-containing heterocycles using a hypervalent iodine(III) reagent. *Chem. Commun.* **1996**, 2225−2226. (b) Wada, Y.; Fujioka, H.; Kita, Y. Synthesis of the Marine Pyrroloiminoquinone Alkaloids, Discorhabdins. *Mar. Drugs* **2010**, *8*, 1394−1416.

(12) (a) Fukuyama, T.; Lu, G. Stereocontrolled Total Synthesis of (±)-Gelsemine. *J. Am. Chem. Soc.* **1996**, *118*, 7426−7427. (b) Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. Total Synthesis of (±)-Gelsemine. *Angew. Chem., Int. Ed.* **1999**, *38*, 2934−2936. (c) Wearing, X. Z.; Cook, J. M. Enantiospecific, Stereospecific Total Synthesis of the Oxindole Alkaloid Alstonisine. *Org. Lett.* **2002**, *4*, 4237−4240. (d) Lin, H.; Danishefsky, S. J. Gelsemine: A Thought-Provoking Target for Total Synthesis. *Angew. Chem., Int. Ed.* **2003**, *4*, 36−51. (e) Marti, C.; Carreira, E. M. Total Synthesis of (−)-Spirotryprostatin B: Synthesis and Related Studies. *J. Am. Chem. Soc.* **2005**, *127*, 11505−11515. (f) Yang, J.; Wearing, X. Z.; le Quesne, P. W.; Deschamps, J. R.; Cook, J. M. Enantiospecific Synthesis of (+)-Alstonisine via a Stereospecific Osmylation Process. *J. Nat. Prod.* **2008**, *71*, 1431−1440. (g) Ma, S.; Han, X.; Krishnan, S.; Virgil, C. S.; Stoltz, M. B. Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles: Facile Access to Oxindoles with C3 All-Carbon Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037−8041. (h) Kulkarni, M. G.; Dhondge, A. P.; Chavhan, S. W.; Borhade, A. S.; Shaikh, Y. B.; Birhade, D. R.; Desai, M. P.; Dhatrak, N. R. Total synthesis of (±)-coerulescine and (±)-horsfiline. *Beilstein J. Org. Chem.* **2010**, *6*, 876−879. (i) Chen, X.; Duan, S.; Tao, C.; Zhai, S.; Qiu, F. G. Total synthesis of (+)-gelsemine via an organocatalytic Diels−Alder approach. *Nat. Commun.* **2015**, *6*, 7204. (j) Zhou, Z.; Xu, Y.; Zhu, B.; Li, P.; Hu, G.; Yang, F.; Xu, S.; Zhang, X. One-pot synthesis of 3-hydroxy-2-oxindoles via acyloin rearrangements of 2-hydroxy-indolin-3-ones generated in situ from 2-alkynyl arylazides. *New J. Chem.* **2020**, *44*, 20303−20307.

(13) (a) Qiao, Z.; Liu, H.; Xiao, X.; Fu, Y.; Wei, J.; Li, Y.; Jiang, X. Efficient Access to 1,4-Benzothiazine: Palladium-Catalyzed Double C−S Bond Formation Using $Na_2S_2O_3$ as Sulfurating Reagent. *Org. Lett.* **2013**, *15*, 2594−2597. (b) Urban, S.; Beiring, B.; Ortega, N.; Paul, D.; Glorius, F. Asymmetric Hydrogenation of Thiophenes and Benzothiophenes. *J. Am. Chem. Soc.* **2012**, *134*, 15241−15244.

(14) (a) Padmavathi, V.; Padmaja, A.; Reddy, D. B. Selena and thiadiazole fused heterocycles. *Indian J. Chem.* **1999**, *38B*, 308−311. (b) Mukherjee, C.; Kamila, S.; De, A. Application of directed metalation in synthesis. Part 4: Expedient synthesis of substituted benzo[b]thiophene and naphthothiophene. *Tetrahedron* **2003**, *59*, 4767−4774. (c) Zweig, J. E.; Newhouse, T. R. Isomer-Specific Hydrogen Bonding as a Design Principle for Bidirectionally Quantitative and Redshifted Hemithioindigo Photoswitches. *J. Am. Chem. Soc.* **2017**, *139*, 10956−10959. (d) Uhl, E.; Thumser, S.; Mayer, P.; Dube, H. Transmission of Unidirectional Molecular Motor Rotation to a Remote Biaryl Axis. *Angew. Chem., Int. Ed.* **2018**, *57*, 11064−11068. (e) Kink, F.; Collado, M. P.; Wiedbrauk, S.; Mayer, P.; Dube, H. Bistable Photoswitching of Hemithioindigo with Green and Red Light: Entry Point to Advanced Molecular Digital Information Processing. *Chem. − Eur. J.* **2017**, *23*, 6237−6243.

(15) (a) Jagodziński, T. S. Thioamides as Useful Synthons in the Synthesis of Heterocycles. *Chem. Rev.* **2003**, *103*, 197−228. (b) Lebel, H. *Product Subclass 7: Thioamides in Science of Synthesis*; Mayer, R.; Scheithauer, S., Eds.; Thieme: Germany, 2005, Vol. *22*, pp. 141−143.

(16) Selected papers (a) Wipf, P.; Venkatraman, S. A New Thiazole Synthesis by Cyclocondensation of Thioamides and Alkynyl(Aryl)-Iodonium Reagents. *J. Org. Chem.* **1996**, *61*, 8004−8005. (b) Kikelj, D.; Urleb, U. Variation 1 : From α-Functionalized Carboxylic Acid Derivatives and Aminothiocarbonyl Compounds. In *Science of Synthesis*; Schaumann, E., Ed.; Thieme: Germany, 2002, Vol. *11*, pp. 643−645; (c) Ishiwata, Y.; Togo, H. Facile Preparation of Thiazoles from 1*H*-1-(1'-Alkynyl)-5-methyl-1,2,3- benziodoxathiole 3,3-Dioxide with Thioamides. *Synlett* **2008**, 2637−2641. (d) Romagnoli, R.; Baraldi, G. P.; Carrion, D. M.; Cruz-Lopez, O.; Lopez Cara, C.; Basso, G.; Viola, G.; Khedr, M.; Balzarini, J.; Mahboobi, S.; Sellmer, A.; Brancale, A.; Hamel, E. 2-Arylamino-4-Amino-5-Aroylthiazoles. "One-Pot" Synthesis and Biological Evaluation of a New Class of Inhibitors of Tubulin Polymerization. *J. Med. Chem.* **2009**, *52*, 5551−5555.

(17) Selected papers (a) Ding, Q.; He, X.; Wu, J. Synthesis of 2-Aminobenzothiazole via Copper(I)-Catalyzed Tandem Reaction of 2-Iodobenzenamine with Isothiocyanate. *J. Comb. Chem.* **2009**, *11*, 587−591. (b) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. Ligand-Free Copper-Catalyzed Synthesis of Substituted Benzimidazoles, 2-Aminobenzimidazoles, 2-Aminobenzothiazoles, and Benzoxazoles. *J. Org. Chem.* **2009**, *74*, 8719−8725. (c) Murru, S.; Ghosh, H.; Sahoo, S. K.; Patel, B. K. Intra- and Intermolecular C-S Bond Formation Using a Single Catalytic System: First Direct Access to Arylthiobenzothiazoles. *Org. Lett.* **2009**, *11*, 4254−4257. (d) Ma, D.; Lu, X.; Shi, L.; Zhang, H.; Jiang, Y.; Liu, X. Domino Condensation/*S*-Arylation/Heterocyclization Reactions: Copper-Catalyzed Three-Component Synthesis of 2-*N*-Substituted Benzothiazoles. *Angew. Chem., Int. Ed.* **2011**, *123*, 1150−1153. (e) Zhang, X.; Zeng, W.; Yang, Y.; Huang, H.; Liang, Y. Copper-Catalyzed Double C−S Bonds Formation via Different Paths: Synthesis of Benzothiazoles from *N*-Benzyl-2-iodoaniline and Potassium Sulfide. *Org. Lett.* **2014**, *16*, 876−879. (f) Dang, P.; Zheng, Z.; Liang, Y. Copper-Catalyzed C(sp^3)−S Bond and C(sp^2)−S Bond Cross-Coupling of 2-(2-Iodobenzoyl) Substituted or 2-(2-Iodobenzyl) Substituted 1,2,3,4-Tetrahydroisoquinolines with Potas-

https://doi.org/10.1021/acsomega.1c03410
ACS Omega 2021, 6, 21169−21180

sium Sulfide: Synthesis of Isoquinoline-Fused 1,3-Benzothiazine Scaffolds. *J. Org. Chem.* **2017**, *82*, 2263−2268. (g) Yugandar, S.; Konda, S.; Ila, H. Synthesis of Substituted Benzo[*b*]thiophenes via Sequential One-Pot, Copper-Catalyzed Intermolecular C−S Bond Formation and Palladium-Catalyzed Intramolecular Arene−Alkene Coupling of Bis(het)aryl/alkyl-1,3-monothiodiketones and o-Bromoiodoarenes. *Org. Lett.* **2017**, *19*, 1512−1515.

(18) Selected papers (a) Tarasova, O. A.; Klyba, L. V.; Vvedensky, V. Y.; Nedolya, N. A.; Trofimov, B. A.; Brandsma, L.; Verkruijsse, H. D. One-Pot Syntheses of 2-*N*-Alkylamino-, 2-*N*-Phenylamino-2-*N*,*N*-Dialkylamino-, and 2-*N*-Alkyl-*N*-phenylaminothiophenes. *Eur. J. Org. Chem.* **1998**, 253−256. (b) Singh, L. W.; Ila, H.; Junjappa, H. Polarized Ketene Dithioacetals. Part 65. Studies on Additions of 2-Aroyl-3-cyano-1,1-bis(methylthio)propenide Anions to Hetero-multiple Bonds. *J. Chem. Soc. Perkin Trans.* **1988**, 2365−2368. (c) Lai, L. L.; Reid, D. H.; Wang, F. L.; Liao, L. F. An Unexpected Synthesis of Thiophene Derivatives by Thionation of *N*-Phenylacetylthio benzamides. *Heteroat. Chem.* **1994**, *5*, 479−486.

(19) Selected papers (a) Kim, Y. S.; Kwak, S. H.; Gong, Y. D. Application of Thio-Ugi Adducts for the Preparation of Benzo[*b*]-thiophene and *S*-Heterocycle Library via Copper Catalyzed Intramolecular C−S Bond Formation. *ACS Comb. Sci.* **2015**, *17*, 365−373. (b) Saraiah, B.; Gautam, V.; Acharya, A.; Pasha, M. A.; Hiriyakkanavar, I. One-Pot Synthesis of 2-(Aryl/Alkyl)amino-3-cyanobenzo[b]thiophenes and Their Hetero-Fused Analogues by Pd-Catalyzed Intramolecular Oxidative C−H Functionalization/Arylthiolation. *Eur. J. Org. Chem.* **2017**, 5679−5688.

(20) Villo, P.; Kervefors, A.; Olofsson, B. Transition metal-free, chemoselective arylation of thioamides yielding aryl thioimidates or *N*-aryl thioamides. *Chem. Commun.* **2018**, *54*, 8810−8813.

(21) Janni, M.; Thirupathi, A.; Arora, S.; Peruncheralathan, S. Chemoselective Ullmann coupling at room temperature: a facile access to 2-aminobenzo[*b*]thiophenes. *Chem. Commun.* **2017**, *53*, 8439−8442.

(22) (a) Janni, M.; Arora, S.; Peruncheralathan, S. Double heteroannulation of S,N-acetals: a facile access to quinolone derivatives. *Org. Biomol. Chem.* **2016**, *14*, 8781−8788. (b) Thirupathi, A.; Janni, M.; Peruncheralathan, S. Copper Catalyzed Intramolecular N-Arylation of Ketene Aminals at Room Temperature: Synthesis of 2-Amino-3-cyanoindoles. *J. Org. Chem.* **2018**, *83*, 8668−8678. (c) Bandyopadhyay, D.; Thirupathi, A.; Dhage, N. M.; Mohanta, N.; Peruncheralathan, S. Nickel catalyzed site selective C−H functionalization of α-aryl-thioamides. *Org. Biomol. Chem.* **2018**, *16*, 6405−6409.

(23) **1a** was treated with LAH affording an intractable mixture of compounds, which could not characterized, whereas in $NaBH_4$ in TFA, **1a** was recovered completely.

(24) (a) Bradsher, C. K.; Edgar, J. K. 1-Substituted Benzocyclobutenes via Parham Cyclialkylation. *J. Org. Chem.* **1981**, *46*, 4600−4602. (b) Guin, J.; Varseev, G.; List, B. Catalytic Asymmetric Protonation of Silyl Ketene Imines. *J. Am. Chem. Soc.* **2013**, *135*, 2100−2103. (c) Yang, X.-Y.; Lin, H.-S.; Matsuo, Y. Highly Selective Synthesis of Tetrahydronapthaleno[60]fullerenes via Fullerene-Cation-Mediated Intramolecular Cyclization. *J. Org. Chem.* **2019**, *84*, 16314−16322.

https://doi.org/10.1021/acsomega.1c03410
ACS Omega 2021, 6, 21169−21180