

HETEROCYCLES, Vol. 68, No. 6, 2006, pp. 1109 - 1119. © The Japan Institute of Heterocyclic Chemistry  
Received, 2nd December, 2005, Accepted, 1st May, 2006, Published online, 2nd May, 2006. COM-05-10644

## SYNTHETIC UTILIZATION OF POLYNITROAROMATIC COMPOUNDS. 4. SYNTHESIS OF NITRO-FREE 4,6-DISUBSTITUTED 3-AMINOBENZOTHIOPHENE DERIVATIVES BASED ON 2,4,6-TRINITROBENZAMIDE

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**Abstract** - A convenient synthesis of nitro-free 4,6-disubstituted 3-aminobenzothiophenes, their *S*-oxides and *S,S*-dioxides based on the available 2,4,6-trinitrobenzamide has been developed. The synthesis entails stepwise nucleophilic substitution of all nitro groups in the starting compound by *S*-, *N*-, and *O*-nucleophiles followed by Thorpe-Ziegler cyclization.

### INTRODUCTION

3-Aminobenzothiophene derivatives are used for the synthesis of various biologically active compounds: protein kinase inhibitors,<sup>1</sup> gyrase inhibitors,<sup>2</sup> adrenoceptor antagonists for symptomatic treatment of benign prostatic hyperplasia,<sup>3</sup> trombine inhibitors,<sup>4</sup> epidermal growth factor tyrosine kinase receptor inhibitors,<sup>5</sup> phosphodiesterase inhibitors,<sup>6</sup> herbicides,<sup>7</sup> and anti-allergics.<sup>8</sup> 3-Aminobenzothiophenes are generally synthesized by Thorpe-Ziegler cyclization of 2-alkylthiobenzonitriles, their *S*-oxides and *S,S*-dioxides.<sup>9-11</sup> The limited availability of functionalized 2-alkylthiobenzonitriles is the major drawback of this approach.

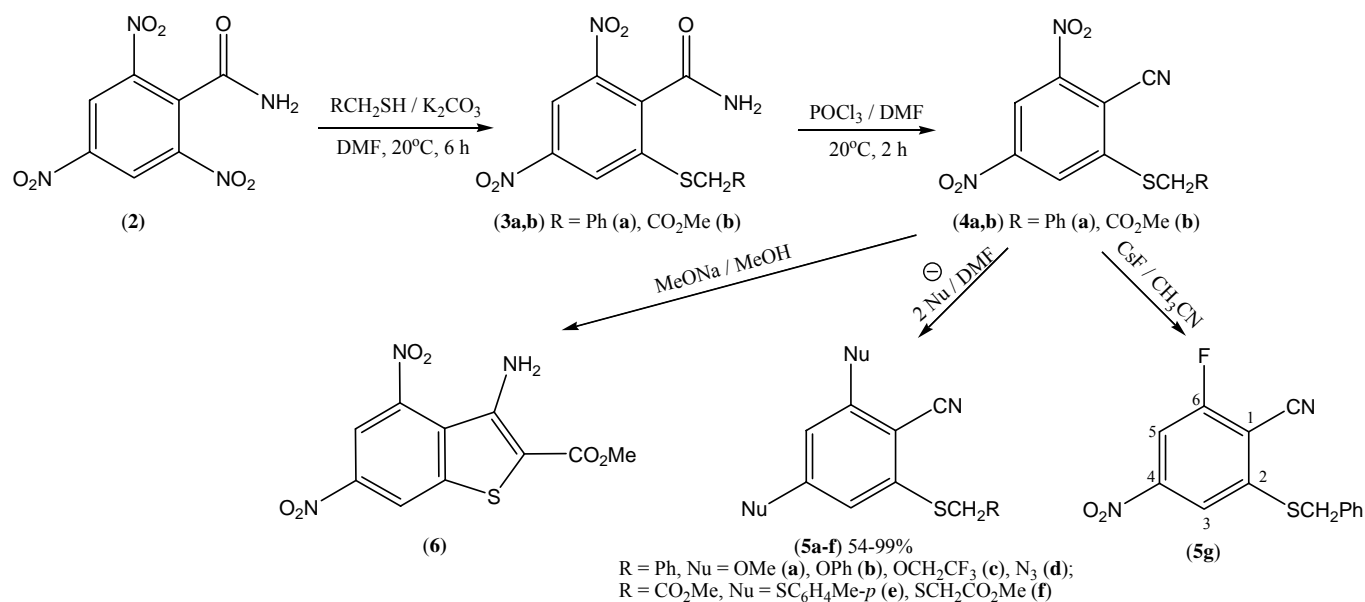
A straightforward approach to the desired compounds includes exhaustive nucleophilic displacement of nitro groups in 2,4,6-trinitrobenzamide (**1**),<sup>12, 13</sup> but regioselectivity remains the major problem.<sup>13</sup>

Alternatively, 2,4,6-trinitrobenzamide (**2**) is reported to react with nucleophiles, yielding 2-substituted 4,6-dinitrobenzamides (**3**),<sup>12, 14</sup> but attempts to remove the remaining nitro groups have failed.<sup>12</sup>

Here we report a successful approach to the convenient synthesis of nitro-free 4,6-disubstituted 3-aminobenzothiophene derivatives based on the available 2,4,6-trinitrobenzamide (**2**). The first step is activation of the nitro groups in the 2-substituted 4,6-dinitrobenzamides (**3**) towards nucleophiles via dehydration to respective nitriles. The second step is replacement of the nitro groups in the 2-substituted 4,6-dinitrobenzonnitriles with *O*-, *S*-, and *N*-nucleophiles followed by a base-promoted Thorpe-Ziegler cyclization of the substitution products (or their *S*-oxides and *S,S*-dioxides).

## RESULTS AND DISCUSSION

2-Substituted 4,6-dinitrobenzamides (**3a,b**) (prepared regioselectively by the reactions of 2,4,6-trinitrobenzamide (**2**) with respective RCH<sub>2</sub>SH / K<sub>2</sub>CO<sub>3</sub> systems in DMF<sup>12, 14</sup>) were dehydrated to 2-substituted 4,6-dinitrobenzonnitriles (**4a,b**) by the Vilsmeier reagent (POCl<sub>3</sub> / DMF<sup>15</sup>) (Scheme 1).

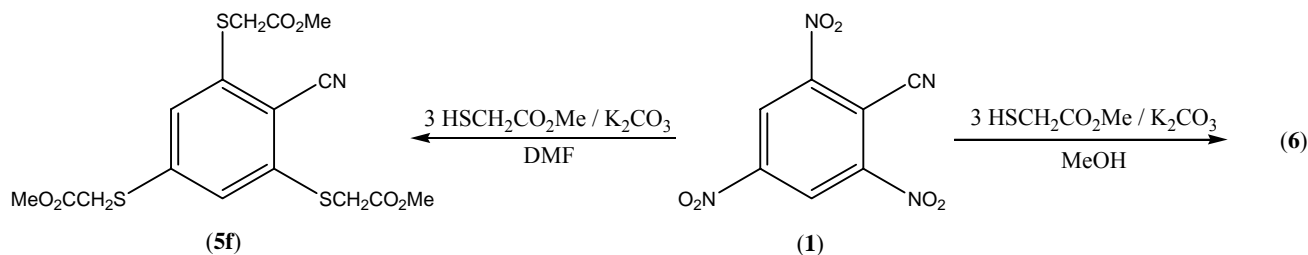


Scheme 1

We studied reactions of the compounds (**4a,b**) with nucleophiles (MeONa, NaN<sub>3</sub>) and with NuH / base systems (RSH / K<sub>2</sub>CO<sub>3</sub>, ROH / K<sub>2</sub>CO<sub>3</sub>) in DMF or in MeOH (in case of MeONa) solutions. Mixtures of C-4/C-6 substitution products were obtained in ~1 : 3 ratio when one molar amount of the nucleophilic reagent was used (<sup>1</sup>H NMR control). We have not been able to separate the isomers because of their similar TLC mobility on silpearl UV-250. Products of the complete displacement of nitro groups (**5a-f**) were obtained only when an excess of *O*-, *N*-, or *S*-nucleophile was used. Cesium fluoride in MeCN was shown to be less reactive: despite of a 5-fold excess of the reagent, only one of the two nitro groups in the compound (**4a**) was replaced by the fluoride anion to afford 2-benzylthio-6-fluoro-4-nitrobenzonnitrile (**5g**). The proposed position of the fluorine atom in **5g** is in agreement with the observed <sup>1</sup>H NMR data:

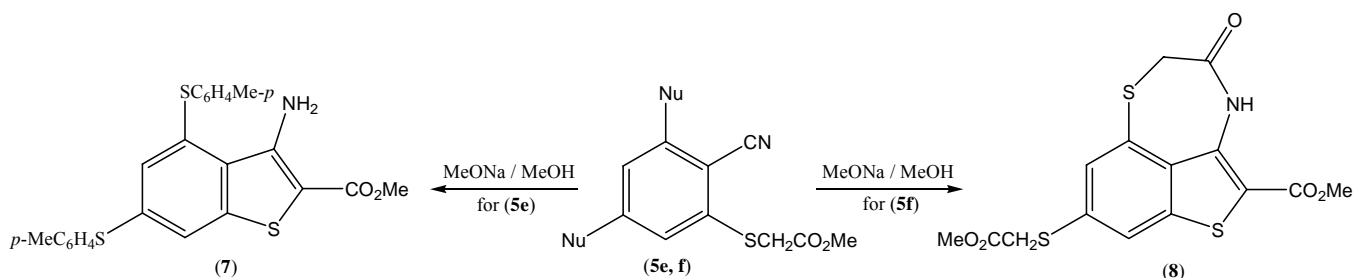
$J_{\text{H-F}}^{1-19}$  with adjacent ( $\text{H}^5$ ,  $\delta$  8.10 ppm) and remote ( $\text{H}^3$ ,  $\delta$  8.17 ppm) protons are 10.0 Hz and  $< 2.0$  Hz, respectively. The observed regioselectivity is in agreement with the reported ortho-selectivity of nucleophilic substitution reactions in 1-R-2,4-dinitro- and 1-R-2,4,6-trinitrobenzenes.<sup>9, 12</sup>

The results of substitution reaction are affected by the nature of both a nucleophile and a solvent. Reactions of the nitrile (**4b**) with  $\text{HSC}_6\text{H}_4\text{Me-4} / \text{K}_2\text{CO}_3$  and  $\text{HSCH}_2\text{CO}_2\text{Me} / \text{K}_2\text{CO}_3$  systems in DMF afforded nitro-free substitution products (**5e, f**), whereas its reaction with MeONa in MeOH gave 3-amino-4,6-dinitrobenzothiophene (**6**). Similar regularities were observed in the reaction of 2,4,6-trinitrobenzonitrile (**1**) with a three-fold excess of methyl  $\alpha$ -mercaptoacetate. The reaction in a DMF solution afforded compound (**5f**), yet in MeOH it yielded a Thorp-Zigler cyclization product (**6**) (Scheme 2). It is possible that due to equilibrium between thiolate- and methylate-anions in MeOH, the latter anion acted as a base initiating cyclization of the intermediate **4b** to the heterocycle **6**.<sup>18</sup>



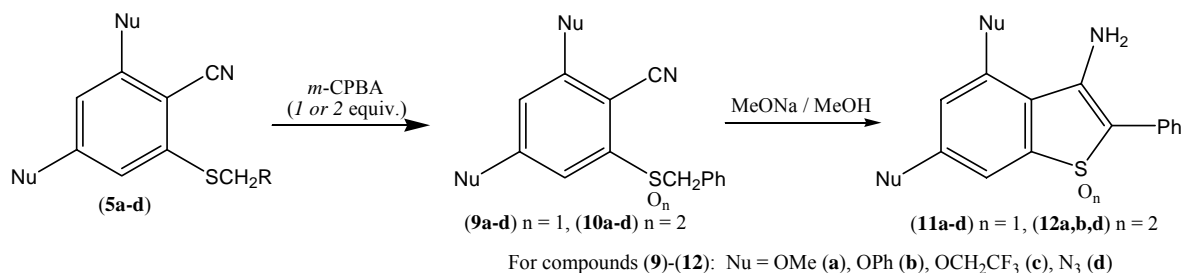
Scheme 2

Substituted benzonitriles (**5a-f**) were found to be convenient building blocks for the synthesis of nitro-free benzothiophene derivatives. A reaction of CH-activated compound (**5e**) with MeONa in MeOH yielded a benzothiophene derivative (**7**) (Scheme 3). Under similar conditions, 2,4,6-tris(methoxycarbonylmethylthio)benzonitrile (**5f**) reacted with MeONa to afford methyl 4,6-bis(*p*-tolylthio)-3-aminobenzo[*b*]thiophene-2-carboxylate (**8**), the first representative of a new heterocyclic system. The reaction entails of a cascade Thorp-Zigler reaction, followed by an intramolecular cyclization of the intermediate benzothiophene derivative with participation of adjacent amino and methoxycarbonyl groups. Attempts to synthesize the nitro-free compounds (**7**) and (**8**) by nucleophilic displacement of the nitro groups in 3-amino-2,4-dinitrobenzothiophene (**6**) failed - an indication of the synthetic value of the proposed methodology.



Scheme 3

Unlike CH-activated nitriles (**5e, f**), 2-benzylthiobenzonitriles (**5a-d**) did not react with MeONa under these conditions. To increase the CH-acidity, they were oxidized to *S*-oxides (**9a-d**) and *S,S*-dioxides (**10a-d**) with *m*-CPBA. The *S*-oxides and *S,S*-dioxides were converted to corresponding 3-aminobenzothiophene derivatives (**11a-d**), (**12a, b, d**) by the action of the MeONa / MeOH system (Scheme 4).



Scheme 4

## CONCLUSIONS

In summary, we have developed a convenient synthesis of 4,6-disubstituted 3-aminobenzothiophenes, their *S*-oxides and *S,S*-dioxides, based on a stepwise nucleophilic displacement of nitro groups in available polynitroaromatic compounds with *O*-, *S*- and *N*- nucleophiles followed by base-promoted cyclization of the reaction products. Although syntheses of fused nitroheterocycles from polynitroaromatic compounds have been reported earlier,<sup>16-20</sup> synthesis of nitro-free heterocycles remains a major challenge.<sup>21</sup> Taking into account that the 2,4,6-trinitrobenzamide (**2**) can be easily prepared from 2,4,6-trinitrotoluene, the proposed method may be considered as an approach to the chemical utilization of polynitroaromatic compounds for the synthesis of valuable chemical products.<sup>12, 14</sup>

## EXPERIMENTAL

<sup>1</sup>H, and <sup>13</sup>C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz {<sup>1</sup>H}) and a Bruker DRX-500 spectrometer (500.13 MHz {<sup>1</sup>H}, 125.76 MHz {<sup>13</sup>C}) in DMSO-*d*<sub>6</sub>. Chemical shifts of <sup>1</sup>H were measured relative to Me<sub>4</sub>Si as the internal standard, <sup>13</sup>C – relative to DMSO-*d*<sub>6</sub>. MS spectra were recorded on a MS-30 (Kratos) instrument (EI). TLC was performed on Silpearl UV-250 silica gel. The compounds (**1**)<sup>22</sup> (**2**), (**3a,b**)<sup>12, 14</sup> were synthesized according to the literature procedures. Solvents were purified by standard methods.

### 2-Benzylthio-4,6-dinitrobenzonitrile (**4a**).

POCl<sub>3</sub> (3.10 mL, 5.19 g, 33.8 mmol) was added to stirred solution of 2-benzylthio-4,6-dinitrobenzamide (**3a**) (8.59 g, 25.8 mmol) in DMF (20 mL) at 0°C. The reaction mixture was allowed to warm up to 20°C, stirred for additional 2 h and then poured into water (100 mL). The precipitate was filtered off, washed

with water, dried in the air, and crystallized from an acetone – *i*-PrOH mixture to give **4a**. Yield 6.42 g (79%), mp 185-187°C. <sup>1</sup>H NMR: δ 4.66 (s, 2H); 7.35 (m, 3H); 7.50 (d, *J* = 8.0 Hz, 2H); 8.61 (s, 1H); 8.63 (s, 1H). *Anal.* Calcd for C<sub>14</sub>H<sub>9</sub>N<sub>3</sub>O<sub>4</sub>S: C, 53.33; H, 2.88; N, 13.33; S, 10.17. Found: C, 53.58; H, 2.72; N, 13.16; S, 9.94.

#### Methyl 2-(2-cyano-3,5-dinitrophenylthio)acetate (**4b**)

This compound was prepared from **3b** (8.13 g, 25.8 mmol) and POCl<sub>3</sub> (3.10 mL, 33.8 mmol) following the same procedure and experimental conditions noted above for **4a**. Yield of **4b** = 6.97 g (91%), mp 93-94°C. <sup>1</sup>H NMR: δ 3.75 (s, 3H); 4.39 (s, 2H); 8.65 (s, 1H); 8.68 (s, 1H). *Anal.* Calcd for C<sub>10</sub>H<sub>7</sub>N<sub>3</sub>O<sub>6</sub>S: C, 40.41; H, 2.37; N, 14.14; S, 10.79. Found: C, 40.69; H, 2.43; N, 13.97; S, 10.57.

#### 2-Benzylthio-4,6-dimethoxybenzonitrile (**5a**)

1-Cyano-2-benzylthio-4,6-dinitrobenzene (**4a**) (0.97 g, 3.08 mmol) was added to a solution of Na (0.30 g, 13.0 mmol) in MeOH (15 mL). The mixture was refluxed for 4 h, cooled to 20°C, poured into water (50 mL), and then adjusted to pH 7 with 10% HCl. The precipitate was filtered off, washed with water, air-dried, and crystallized from *i*-PrOH to give **5a**. Yield 0.81 g (92%), mp 105-107°C. <sup>1</sup>H NMR: δ 3.82 (s, 3H); 3.87 (s, 3H); 4.31 (s, 2H); 6.44 (s, 1H); 6.55 (s, 1H); 7.30 (m, 4H); 7.40 (t, *J* = 8.0 Hz, 1H). <sup>13</sup>C NMR: δ 35.71, 55.98, 56.52, 95.86, 101.81, 105.18, 114.75, 127.36, 128.50, 128.86, 136.18, 144.07, 163.34, 163.89. MS (*m/z*, I): 285 (M<sup>+</sup>, 68%), 270 (3%), 256 (7%), 194 (7%), 150 (10%), 91 (100%). *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>2</sub>S: C, 67.34; H, 5.30; N, 4.91; S, 11.24. Found: C, 67.10; H, 5.23; N, 5.04; S, 11.13.

#### 2-Benzylthio-4,6-diphenoxybenzonitrile (**5b**)

Phenol (1.00 g, 10.6 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.50 g, 10.9 mmol) were added successively to stirred solution of **4a** (0.97 g, 3.08 mmol) in DMF (15 mL). The reaction mixture was stirred at 80°C for 6 h, cooled to 20°C, poured into water (100 mL), and then adjusted to pH 7 with 10% HCl. The aqueous layer was decanted from black oil. Acetone - CCl<sub>4</sub> (1 : 1 v/v) mixture (20 mL) was added to the residue and evaporated to dryness under reduced pressure. The procedure was repeated twice. Crystallization of the residue from *i*-PrOH gave **5b**. Yield 1.16 g (92%), mp 75-81°C. <sup>1</sup>H NMR: δ 4.28 (s, 2H); 6.13 (s, 1H); 6.69 (s, 1H); 6.99 (d, *J* = 8.0 Hz, 2H); 7.10 (d, *J* = 8.0 Hz, 2H); 7.22-7.32 (m, 7H); 7.38-7.45 (m, 4H). <sup>13</sup>C NMR: δ 35.65, 95.32, 102.44, 109.79, 113.79, 119.65, 120.05, 125.30, 125.36, 127.34, 128.50, 128.64, 128.71, 130.32, 135.78, 145.51, 153.65, 154.04, 161.52, 161.77. MS (*m/z*, I): 409 (M<sup>+</sup>, 30%), 318 (15%), 91 (100%). *Anal.* Calcd for C<sub>26</sub>H<sub>19</sub>NO<sub>2</sub>S: C, 76.26; H, 4.68; N, 3.42; S, 7.83. Found: C, 75.99; H, 4.60; N, 3.55; S, 7.68.

#### 2,4-Bis(2,2,2-trifluoroethoxy)-6-(benzylthio)benzonitrile (**5c**)

2,2,2-Trifluoroethanol (2.00 mL, 2.79 g, 27.9 mmol) and K<sub>2</sub>CO<sub>3</sub> (2.70 g, 19.6 mmol) were added successively to stirred solution of **4a** (1.51 g, 4.80 mmol) in DMF (10 mL). The reaction mixture was stirred at 90°C for 6 h, cooled to 20°C and poured into water (100 mL). The precipitate was filtered off, washed with water, air-dried, and crystallized from *i*-PrOH to give **5c**. Yield 1.25 g (62%), mp 73-76°C.

$^1\text{H}$  NMR:  $\delta$  4.34 (s, 2H); 4.72 (q,  $J_{\text{H-F}} = 8.0$  Hz, 2H); 4.76 (q,  $J_{\text{H-F}} = 8.0$  Hz, 2H); 6.77 (s, 1H); 6.85 (s, 1H); 7.25 (t,  $J = 7.5$  Hz, 1H); 7.32 (t,  $J = 7.5$  Hz, 2H); 7.40 (d,  $J = 7.5$  Hz, 2H). MS ( $m/z$ , I): 421 ( $\text{M}^+$ , 15%), 330 (3%), 309 (4%), 266 (4%), 91 (100%). *Anal.* Calcd for  $\text{C}_{18}\text{H}_{13}\text{NO}_2\text{F}_6\text{S}$ : C, 51.31; H, 3.11; N, 3.32; F, 27.05; S, 7.61. Found: C, 51.56; H, 3.28; N, 3.49; F, 26.83; S, 7.44.

#### 2,4-Diazido-6-(benzylthio)benzonitrile (5d)

$\text{NaN}_3$  (1.50 g, 23.1 mmol) was added to a solution of **4a** (1.26 g, 4.00 mmol) in DMF (10 mL). The reaction mixture was stirred at  $50^\circ\text{C}$  for 6 h, cooled to  $20^\circ\text{C}$  and poured into water (100 mL). The precipitate was filtered off, washed with water, air-dried, and crystallized from acetone - *i*-PrOH mixture to give **5d**. Yield 1.17 g (95%), mp  $119\text{--}120^\circ\text{C}$ .  $^1\text{H}$  NMR:  $\delta$  4.39 (s, 2H); 6.90 (s, 2H); 7.28 (t,  $J = 8.0$  Hz, 1H); 7.32 (t,  $J = 8.0$  Hz, 2H); 7.40 (d,  $J = 8.0$  Hz, 2H). *Anal.* Calcd for  $\text{C}_{14}\text{H}_9\text{N}_7\text{S}$ : C, 54.71; H, 2.95; N, 31.90; S, 10.43. Found: C, 54.95; H, 3.03; N, 31.67; S, 10.29.

#### Methyl 2-(3,5-bis(*p*-tolylthio)-2-cyanophenylthio)acetate (5e)

4-Methylthiophenol (0.18 g, 1.45 mmol) and  $\text{K}_2\text{CO}_3$  (0.20 g, 1.45 mmol) were added successively to a solution of **4b** (0.20 g, 0.67 mmol) in DMF (8 mL). The reaction mixture was stirred at  $25^\circ\text{C}$  for 5 h, cooled to  $20^\circ\text{C}$ , and poured into water (50 mL). The precipitate was filtered off, washed with water, air-dried, and crystallized from benzene to give **5e**. Yield 0.17 g (60%), mp  $135\text{--}137^\circ\text{C}$ .  $^1\text{H}$  NMR:  $\delta$  2.38 (s, 6H); 3.66 (s, 3H); 4.12 (s, 2H); 6.00 (s, 1H); 7.04 (s, 1H); 7.14-7.37 (m, 8H). *Anal.* Calcd for  $\text{C}_{24}\text{H}_{21}\text{NO}_2\text{S}_3$ : C, 63.83; H, 4.69; N, 3.10; S, 21.30. Found: C, 64.04; H, 4.80; N, 2.98; S, 21.11.

#### 2,4,6-tris(methoxycarbonylmethylthio)benzonitrile (5f)

**Method A.** Methyl  $\alpha$ -mercaptoacetate (0.13 mL, 0.15 g, 1.43 mmol) and  $\text{K}_2\text{CO}_3$  (0.20 g, 1.45 mmol) were added successively to a solution of **4b** (0.20 g, 0.67 mmol) in DMF (8 mL). The reaction mixture was stirred at  $25^\circ\text{C}$  for 5 h and poured into water (50 mL). The precipitate was filtered off, washed with water, air-dried, and crystallized from benzene to give **5f**. Yield 0.22 g (77%), mp  $85\text{--}86^\circ\text{C}$  (lit.,<sup>12</sup> mp  $84\text{--}86^\circ\text{C}$ ).  $^1\text{H}$  NMR:  $\delta$  3.72 (s, 9H); 4.02 (s, 6H); 7.21 (s, 2H).

**Method B.** This compound was prepared from **1** (1.00 g, 4.40 mmol), methyl  $\alpha$ -mercaptoacetate (1.60 g, 15.3 mmol) and  $\text{K}_2\text{CO}_3$  (2.12 g, 15.3 mmol) in DMF following the procedure and experimental conditions described in the literature.<sup>12</sup>

#### 2-Benzylthio-6-fluoro-4-nitrobenzonitrile (5g)

2-Benzylthio-4,6-dinitrobenzonitrile (**4a**) (0.10 g, 0.32 mmol) was added to a suspension of freshly dried CsF (0.25 g, 1.64 mmol) in dry MeCN (5 mL). The reaction mixture was refluxed for 4 h and evaporated under reduced pressure. Water (2 mL) was added to the residue. The precipitate was filtered off, washed with water, air-dried, and crystallized from benzene to give **5g**. Yield 0.05 g (54%), mp  $122\text{--}125^\circ\text{C}$ .  $^1\text{H}$  NMR:  $\delta$  4.60 (s, 2H); 7.30 (t,  $J = 8.0$  Hz, 1H); 7.35 (t,  $J = 8.0$  Hz, 2H); 7.45 (d,  $J = 8.0$  Hz, 2H); 8.10 (d,  $J_{\text{H-F}} = 10$  Hz, 1H); 8.17 (s, 1H). MS ( $m/z$ , I): 288 ( $\text{M}^+$ , 5%), 197 (2%), 91 (100%). *Anal.* Calcd for

C<sub>14</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub>FS: C, 58.33; H, 3.15; N, 9.72; F, 6.59; S, 11.12. Found: C, 58.09; H, 3.00; N, 9.87; F, 6.38; S, 10.95.

### Methyl 3-amino-4,6-dinitrobenzo[*b*]thiophene-2-carboxylate (6)

**Method A.** **4b** (0.56 g, 1.90 mmol) was added to a solution of sodium (0.17 g, 7.39 mmol) in MeOH (5 mL). The reaction mixture was stirred for 10 min at 20°C, diluted with water to 50 mL, and adjusted to pH 7 with 10% HCl. The precipitate was filtered off, washed with water, air-dried, and crystallized from acetone – *i*-PrOH mixture to give **6**. Yield 0.53 g (95%), mp 195-197°C (lit.,<sup>13</sup> mp 196-198°C). <sup>1</sup>H NMR: δ 3.91 (s, 3H); 6.59 (s, 2H); 8.66 (s, 1H); 9.30 (s, 1H).

**Method B.** Methyl α-mercaptoacetate (0.30 mL, 0.35 g, 3.29 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.45 g, 3.26 mmol) were added successively to a solution of 1-cyano-2,4,6-trinitrobenzene (**1**) (0.37 g, 1.55 mmol) in MeOH (5 mL). The reaction mixture was stirred at 20°C for 1 h, poured into water (20 mL), and adjusted to pH 7 with 10% HCl. The precipitate was filtered off, washed with water, air-dried and crystallized from EtOH to give **6**. Yield 0.33 g (72%), mp 196-198°C.

### Methyl 4,6-bis(*p*-tolylthio)-3-aminobenzo[*b*]thiophene-2-carboxylate (7)

The nitrile (**5e**) (0.14 g, 0.31 mmol) was added to KOH (0.05 g, 0.89 mmol) solution in MeOH (6 mL). The reaction mixture was stirred at 35°C for 4 h, the precipitate was filtered off, washed with water (3 × 7 mL), air-dried, and crystallized from the benzene-THF mixture to afford the **7**. Yield 0.10 g (74%), mp 141-142°C. <sup>1</sup>H NMR: δ 2.23 (s, 6H); 3.72 (s, 3H); 6.80 (s, 1H); 7.01-7.27 (m, 10H); 7.53 (s, 1H). *Anal.* Calcd for C<sub>24</sub>H<sub>21</sub>NO<sub>2</sub>S<sub>3</sub>: C, 63.83; H, 4.69; N, 3.10; S, 21.30. Found: C, 63.60; H, 4.54; N, 3.23; S, 21.45.

### Methyl 4,5-dihydro-8-(methoxycarbonylmethylthio)-4-oxo-3*H*-thieno[4,3,2-*ef*][1,4]benzothiazepine-2-carboxylate (8)

2,4,6-Tris(methoxycarbonylmethylthio)benzotrile (**5f**) (0.50 g, 1.20 mmol) was added to a solution of Na (0.06 g, 2.61 mmol) in MeOH (10 mL). The reaction mixture was stirred at 20°C for 2 h, diluted with water (40 mL) and adjusted to pH 7 with 10% HCl. The precipitate was filtered off, washed with water, air-dried, and crystallized from acetone – *i*-PrOH mixture to give **8**. Yield 0.27 g (58%), mp 150-152°C. <sup>1</sup>H NMR: δ 3.68 (s, 3H); 3.87 (s, 2H); 3.91 (s, 3H); 4.05 (s, 2H); 7.40 (s, 1H); 7.83 (s, 1H); 10.04 (s, 1H). <sup>13</sup>C NMR: δ 33.64, 35.50, 52.34, 52.56, 109.15, 119.37, 123.95, 127.87, 134.42, 136.67, 138.48, 141.43, 163.65, 168.76, 169.23. MS (*m/z*, I): 383 (M<sup>+</sup>, 100%), 350 (20%), 323 (25%). *Anal.* Calcd for C<sub>15</sub>H<sub>13</sub>NO<sub>5</sub>S<sub>3</sub>: C, 46.98; H, 3.42; N, 3.65; S, 25.09. Found: C, 47.23; H, 3.57; N, 3.48; S, 24.90.

### 4,6-Disubstituted 2-(benzylsulfinyl)benzotrile (9a-d) and 4,6-disubstituted 2-(benzylsulfonyl)benzotrile (10a-d) (General procedure)

*m*-CPBA (86% purity, 0.79 g, 3.92 mmol for (**9a-d**) or 1.60 g, 7.94 mmol for (**10a-d**)] was added to a solution of 4,6-disubstituted 1-cyano-2-alkylthiobenzene (**5a-d**) (3.92 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0°C. The reaction mixture was stirred at 20°C for 2 h (TLC-monitoring) and adjusted to pH 7 with saturated

NaHCO<sub>3</sub> water solution. The aqueous layer was separated, extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and discarded. Combined organic layers were dried over anhydrous MgSO<sub>4</sub> and evaporated to dryness. The solid residue was crystallized from *i*-PrOH to give **9a-d** or **10a-d**. The following compounds were obtained:

**2-(Benzylsulfinyl)-4,6-dimethoxybenzonitrile (9a)**

Yield 90%, mp 126-128°C. <sup>1</sup>H NMR: δ 3.30 (s, 3H); 3.96 (s, 3H); 4.03 (d, *J* = 13.9 Hz, 1H); 4.38 (d, *J* = 13.9 Hz, 1H); 6.60 (s, 1H); 6.81 (s, 1H); 7.06 (d, *J* = 8.0 Hz, 2H); 7.30 (m, 3H). <sup>13</sup>C NMR: δ 56.24, 57.02, 60.69, 88.68, 100.92, 102.55, 113.05, 128.14, 129.21, 130.33, 149.57, 163.15, 164.44. MS (*m/z*, I): 301 (M<sup>+</sup>, 10%), 285 (2%), 210 (5%), 91 (100%). *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>3</sub>S: C, 63.77; H, 5.02; N, 4.65; S, 10.64. Found: C, 63.54; H, 5.16; N, 4.48; S, 10.41.

**2-(Benzylsulfinyl)-4,6-diphenoxybenzonitrile (9b)**

Yield 78%, mp 156-159°C. <sup>1</sup>H NMR: δ 4.17 (d, *J* = 12.5 Hz, 1H); 4.50 (d, *J* = 12.5 Hz, 1H); 6.49 (s, 1H); 6.53 (s, 1H); 6.81 (d, *J* = 8.0 Hz, 2H); 7.02 (d, *J* = 8.0 Hz, 2H); 7.23 (m, 3H); 7.30-7.45 (m, 6H); 7.50 (t, *J* = 8.0 Hz, 2H). <sup>13</sup>C NMR: δ 59.91, 92.68, 107.13, 107.72, 112.26, 119.64, 120.18, 125.62, 125.75, 128.11, 128.19, 128.46, 130.32, 130.46, 150.38, 153.17, 154.23, 161.33, 162.24. MS (*m/z*, I): 425 (M<sup>+</sup>, 2%), 409 (2%), 334 (2%), 317 (2%), 285 (5%), 91 (100%). *Anal.* Calcd for C<sub>26</sub>H<sub>19</sub>NO<sub>3</sub>S: C, 73.39; H, 4.50; N, 3.29; S, 7.54. Found: C, 73.59; H, 4.63; N, 3.23; S, 7.40.

**2,4-Bis(2,2,2-trifluoroethoxy)-6-(benzylsulfinyl)benzonitrile (9c)**

Yield 80%, mp 127-128°C. <sup>1</sup>H NMR: δ 4.04 (d, *J* = 12.5 Hz, 1H); 4.33 (d, *J* = 12.5 Hz, 1H); 4.63 (m, *J*<sub>H-H</sub> = 10 Hz, *J*<sub>H-F</sub> = 8.3 Hz, 1H); 4.77 (m, *J*<sub>H-H</sub> = 10 Hz, *J*<sub>H-F</sub> = 8.3 Hz, 1H); 4.89 (m, *J*<sub>H-F</sub> = 8.3 Hz, 2H); 6.87 (s, 1H); 7.30 (s, 1H); 7.24 - 7.40 (m, 5H). MS (*m/z*, I): 437 (M<sup>+</sup>, 5%), 421 (3%), 346 (15%), 331 (5%), 91 (100%). *Anal.* Calcd for C<sub>18</sub>H<sub>13</sub>NO<sub>3</sub>F<sub>6</sub>S: C, 49.43; H, 3.00; N, 3.20; F, 26.06; S, 7.33. Found: C, 49.62; H, 3.08; N, 3.07; F, 25.89; S, 7.20.

**2,4-Diazido-6-(benzylsulfinyl)benzonitrile (9d)**

Yield 84%, mp 164-167°C. <sup>1</sup>H NMR: δ 4.13 (d, *J* = 13.9 Hz, 1H); 4.42 (d, *J* = 13.9 Hz, 1H); 6.87 (s, 1H); 7.08 (d, *J* = 8.0 Hz, 2H); 7.26-7.35 (m, 4H). MS (*m/z*, I): 323 (M<sup>+</sup>, 10%), 91 (100%). *Anal.* Calcd for C<sub>14</sub>H<sub>9</sub>N<sub>7</sub>OS: C, 52.01; H, 2.81; N, 30.32; S, 9.92. Found: C, 52.25; H, 2.93; N, 30.18; S, 9.84.

**2-(Benzylsulfonyl)-4,6-dimethoxybenzonitrile (10a)**

Yield 83%, mp 169-172°C. <sup>1</sup>H NMR: δ 3.88 (s, 3H); 4.03 (s, 3H); 4.70 (s, 2H); 6.85 (s, 1H); 7.01 (s, 1H); 7.23 (d, *J* = 8.0 Hz, 2H); 7.32 (m, 3H). <sup>13</sup>C NMR: δ 56.58, 57.41, 60.16, 90.79, 102.93, 108.89, 113.10, 127.34, 128.56, 128.69, 130.98, 142.30, 163.51, 164.46. MS (*m/z*, I): 317 (M<sup>+</sup>, 3%), 254 (5%), 253 (40%), 238 (8%), 210 (13%), 91 (100%). *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>4</sub>S: C, 60.55; H, 4.76; N, 4.41; S, 10.10. Found: C, 60.37; H, 4.62; N, 4.55; S, 9.94.

**2-(Benzylsulfonyl)-4,6-diphenoxybenzonitrile (10b)**



Yield 82%, mp 181-184 °C.  $^1\text{H}$  NMR:  $\delta$  4.80 (s, 2H); 6.70 (s, 1H); 6.85 (s, 1H); 6.95 (d,  $J = 8.0$  Hz, 2H); 7.20-7.28 (m, 5H); 7.30 (t,  $J = 8.0$  Hz, 1H); 7.36-7.43 (m, 5H); 7.50 (t,  $J = 8.0$  Hz, 2H). *Anal.* Calcd for  $\text{C}_{26}\text{H}_{19}\text{NO}_4\text{S}$ : C, 70.73; H, 4.34; N, 3.17; S, 7.26. Found: C, 70.97; H, 4.49; N, 3.06; S, 7.10. MS ( $m/z$ , I): 441 ( $\text{M}^+$ , 2%), 377 (30%); 91 (100%).

#### **2,4-Bis(2,2,2-trifluoroethoxy)-6-(benzylsulfonyl)benzonitrile (10c)**

Yield 91%, mp 132-134°C.  $^1\text{H}$  NMR:  $\delta$  4.69 (s, 2H); 4.81 (q,  $J_{\text{H-F}} = 8.0$  Hz, 2H); 4.94 (q,  $J_{\text{H-F}} = 8.0$  Hz, 2H); 7.12 (s, 1H); 7.27 - 7.32 (m, 5H); 7.43 (s, 1H). MS ( $m/z$ , I): 453 ( $\text{M}^+$ , 5%), 439 (2%), 390 (14%), 389 (100%), 320 (5%), 91 (100%). *Anal.* Calcd for  $\text{C}_{18}\text{H}_{13}\text{NO}_4\text{F}_6\text{S}$ : C, 47.69; H, 2.89; N, 3.09; F, 25.14; S, 7.07. Found: C, 47.87; H, 3.01; N, 2.96; F, 24.95; S, 7.00.

#### **2,4-Diazido-6-(benzylsulfonyl)benzonitrile (10d)**

Yield 80%, mp 203-206°C.  $^1\text{H}$  NMR:  $\delta$  4.80 (s, 2H); 7.20 (d,  $J = 8.0$  Hz, 2H); 7.34 (m, 3H); 7.48 (s, 1H); 7.61 (s, 1H). *Anal.* Calcd for  $\text{C}_{14}\text{H}_9\text{N}_7\text{O}_2\text{S}$ : C, 49.55; H, 2.67; N, 28.89; S, 9.45. Found: C, 49.77; H, 2.73; N, 28.68; S, 9.31.

#### **4,6-Disubstituted 2-phenylbenzo[*b*]thiophen-3-amine-1-oxides (11a-d) and 1,1-dioxides (12a, b, d) (General procedure)**

*S*-Oxide (**9a-d**) or *S,S*-dioxide (**10a-d**) (1.98 mmol) was added to a solution of Na (0.10 g, 4.35 mmol) in MeOH (10 mL). The reaction mixture was stirred at 65°C for 4 h and evaporated in *vacuo* to dryness. Water (20 mL) was added to the residue, and the mixture was acidified to pH 2 with 10% HCl. The precipitate was filtered off, washed with water, air-dried, and crystallized from acetone – *i*-PrOH mixture to give **11a-d** or **12a, b, d**. The following compounds were obtained:

#### **4,6-Dimethoxy-2-phenylbenzo[*b*]thiophen-3-amine-1-oxide (11a)**

Yield 84%, mp 163-166°C.  $^1\text{H}$  NMR:  $\delta$  3.91 (s, 3H); 3.99 (s, 3H); 6.36 (s, 2H); 6.80 (s, 1H); 7.10 (s, 1H); 7.22 (t,  $J = 8.0$  Hz, 1H); 7.41 (t,  $J = 8.0$  Hz, 2H); 7.55 (d,  $J = 8.0$  Hz, 2H). MS ( $m/z$ , I): 301 ( $\text{M}^+$ , 30%), 285 (25%), 224 (30%), 196 (100%), 105 (20%), 77 (45%). *Anal.* Calcd for  $\text{C}_{16}\text{H}_{15}\text{NO}_3\text{S}$ : C, 63.77; H, 5.02; N, 4.65; S, 10.64. Found: C, 63.55; H, 4.97; N, 4.81; S, 10.49.

#### **4,6-Diphenoxy-2-phenylbenzo[*b*]thiophen-3-amine-1-oxide (11b)**

Yield 71%, mp 172-175°C.  $^1\text{H}$  NMR:  $\delta$  6.40 (s, 2H); 6.49 (s, 1H); 7.11 (d,  $J = 8.0$  Hz, 2H); 7.21 (m, 2H); 7.26 (m, 4H); 7.42-7.48 (m, 6H); 7.57 (d,  $J = 8.0$  Hz, 2H). MS ( $m/z$ , I): 425 ( $\text{M}^+$ , 30%), 409 (30%), 348 (25%), 320 (100%), 105 (30%), 77 (100%). *Anal.* Calcd for  $\text{C}_{26}\text{H}_{19}\text{NO}_3\text{S}$ : C, 73.39; H, 4.50; N, 3.29; S, 7.54. Found: C, 73.15; H, 4.44; N, 3.41; S, 7.40.

#### **4,6-Bis(2,2,2-trifluoroethoxy)-2-phenylbenzo[*b*]thiophen-3-amine-1-oxide (11c)**

Yield 64%, mp 179-182°C.  $^1\text{H}$  NMR:  $\delta$  4.94 (q,  $J_{\text{H-F}} = 8.0$  Hz, 2H); 5.13 (q,  $J_{\text{H-F}} = 8.0$  Hz, 2H) 6.34 (s, 2H); 7.18 (s, 1H); 7.19 (s, 1H); 7.26 (t,  $J = 8.0$  Hz, 1H); 7.43 (t,  $J = 8.0$  Hz, 2H); 7.56 (d,  $J = 8.0$  Hz, 2H).  $^{13}\text{C}$  NMR:  $\delta$  65.3 (q,  $^2J_{\text{C-F}} = 33.9$  Hz), 104.7, 106.5, 109.9, 115.5, 123.7 (q,  $^1J_{\text{C-F}} = 277.9$  Hz), 125.8,

127.3, 128.9, 132.4, 143.2, 148.1, 153.4, 159.1. *Anal.* Calcd for C<sub>18</sub>H<sub>13</sub>NO<sub>3</sub>F<sub>6</sub>S: C, 49.43; H, 3.00; N, 3.20; F, 26.06; S, 7.33. Found: C, 49.31; H, 2.96; N, 3.29; F, 25.93; S, 7.18.

#### **4,6-Diazido-2-phenylbenzo[*b*]thiophen-3-amine-1-oxide (11d)**

Yield 80%, mp 203-206°C. <sup>1</sup>H NMR: δ 4.80 (s, 2H); 7.20 (d, *J* = 8.0 Hz, 2H); 7.34 (m, 3H); 7.48 (s, 1H); 7.61 (s, 1H). MS (*m/z*, I): 323 (M<sup>+</sup>, 30%), 307 (10%), 266 (5%), 251 (10%), 238 (10%), 218 (5%), 105 (100%), 77 (80%). *Anal.* Calcd for C<sub>14</sub>H<sub>9</sub>N<sub>7</sub>OS: C, 52.01; H, 2.81; N, 30.32; S, 9.92. Found: C, 51.84; H, 2.89; N, 30.18; S, 9.77.

#### **4,6-Dimethoxy-2-phenylbenzo[*b*]thiophen-3-amine-1,1-dioxide (12a)**

Yield 88%, mp 206-209°C. <sup>1</sup>H NMR: δ 3.93 (s, 3H); 4.01 (s, 3H); 6.61 (s, 2H); 6.82 (s, 1H); 6.97 (s, 1H); 7.28 (t, *J* = 8.0 Hz, 1H); 7.42 (t, *J* = 8.0 Hz, 2H); 7.58 (d, *J* = 8.0 Hz, 2H). *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>4</sub>S: C, 60.55; H, 4.76; N, 4.41; S, 10.10. Found: C, 60.72; H, 4.69; N, 4.45; S, 9.98.

#### **4,6-Diphenoxy-2-phenylbenzo[*b*]thiophen-3-amine-1,1-dioxide (12b)**

Yield 94%, mp 169-171°C. <sup>1</sup>H NMR: δ 6.45 (s, 1H); 6.74 (s, 2H); 7.04 (s, 1H); 7.13 (d, *J* = 8.0 Hz, 2H); 7.22 (t, *J* = 8.0 Hz, 1H); 7.28 (m, 3H); 7.34 (t, *J* = 8.0 Hz, 1H); 7.44 (t, *J* = 8.0 Hz, 2H); 7.46 (t, *J* = 8.0 Hz, 2H); 7.48 (t, *J* = 8.0 Hz, 2H); 7.59 (d, *J* = 8.0 Hz, 2H). MS (*m/z*, I): 441 (M<sup>+</sup>, 60%), 409 (10%), 336 (15%), 319 (15%), 105 (40%), 77 (100%). *Anal.* Calcd for C<sub>26</sub>H<sub>19</sub>NO<sub>4</sub>S: C, 70.73; H, 4.34; N, 3.17; S, 7.26. Found: C, 70.94; H, 4.42; N, 3.02; S, 7.17.

#### **4,6-Diazido-2-phenylbenzo[*b*]thiophen-3-amine-1,1-dioxide (12d)**

Yield 70%, mp 190-192°C. <sup>1</sup>H NMR: δ 6.72 (s, 2H); 7.25 (s, 1H); 7.30 (t, *J* = 8.0 Hz, 1H); 7.47 (t, *J* = 8.0 Hz, 2H); 7.50 (s, 1H); 7.60 (d, *J* = 8.0 Hz, 2H). *Anal.* Calcd for C<sub>14</sub>H<sub>9</sub>N<sub>7</sub>O<sub>2</sub>S: C, 49.55; H, 2.67; N, 28.89; S, 9.45. Found: C, 49.73; H, 2.79; N, 28.66; S, 9.31.

## **ACKNOWLEDGEMENTS**

This research was sponsored by the IPP program. Oak Ridge National Laboratory is managed and operated by UT-Battelle, LLC, under contract DE-AC05-00OR22725 for the U.S. Department of Energy. Contribution 15, the Discovery Chemistry Project.

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