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

Sergei G. Zlotin,[a]* Pavel G. Kislitsin,[a] Fedor A. Kucherov,[a] and Andrei A. Gakh[b]*

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, Moscow, 119991, Russia; e-mail: zlotin@ioc.ac.ru*

[b] *Oak Ridge National Laboratory, Oak Ridge, TN 37831-6242, USA; e-mail: gakhaa@ornl.gov*

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,[1] gyrase inhibitors,[2] adrenoceptor antagonists for symptomatic treatment of bening prostatic hyperplasma,[3] trombine inhibitors,[4] epidermal growth factor tyrosine kinase receptor inhibitors,[5] phosphodiesterase inhibitors,[6] herbicides,[7] and antiallergetics.[8] 3-Aminobenzothiophenes are generally synthesized by Thorpe-Ziegler cyclization of 2-alkylthiobenzonitriles, their *S*-oxides and *S*,*S*-dioxides.[9–11] The limited availability of functionalized 2-alkylthiobenzonitriles is the major drawback of this approach.

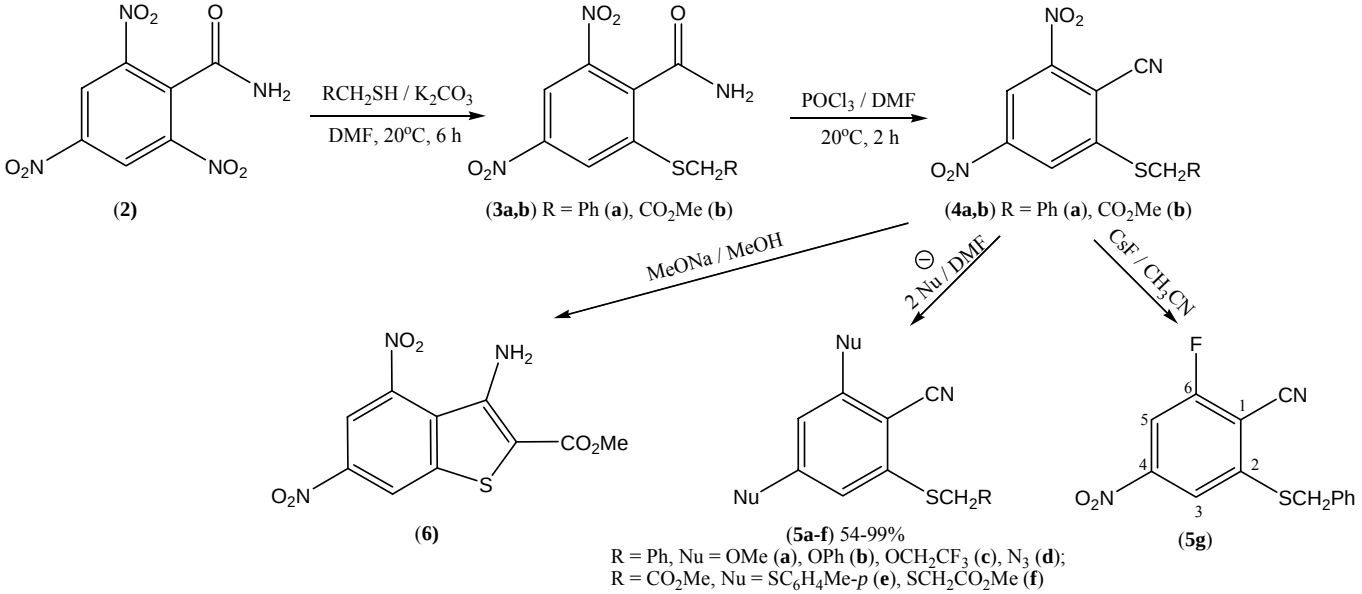
A straightforward approach to the desired compounds includes exhaustive nucleophilic displacement of nitro groups in 2,4,6-trinitrobenzonitrile (**1**),[12, 13] but regioselectivity remains the major problem.[13]

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

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-dinitrobenzonitriles 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_2SH / K_2CO_3 systems in DMF[12, 14]) were dehydrated to 2-substituted 4,6-dinitrobenzonitriles (**4a,b**) by the Vilsmeier reagent ($POCl_3$ /DMF[15]) (Scheme 1).

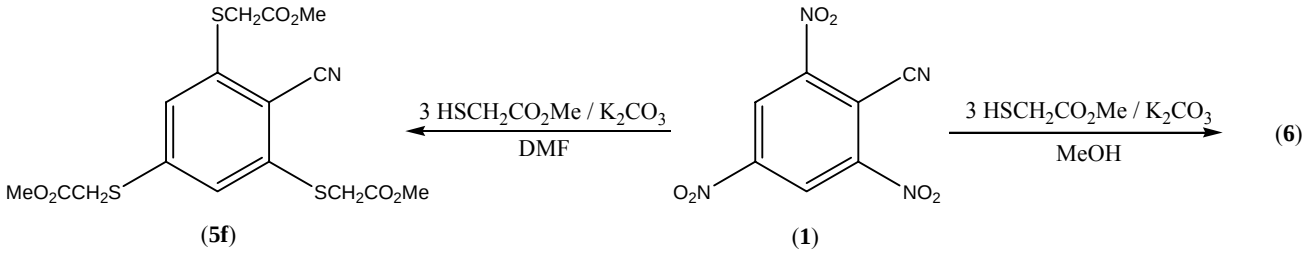


Scheme 1

We studied reactions of the compounds (**4a,b**) with nucleophiles (MeONa, NaN_3) and with NuH / base systems (RSH / K_2CO_3, ROH / K_2CO_3) 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 (^{1}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-nitrobenzonitrile (**5g**). The proposed position of the fluorine atom in **5g** is in agreement with the observed ^{1}H NMR data:

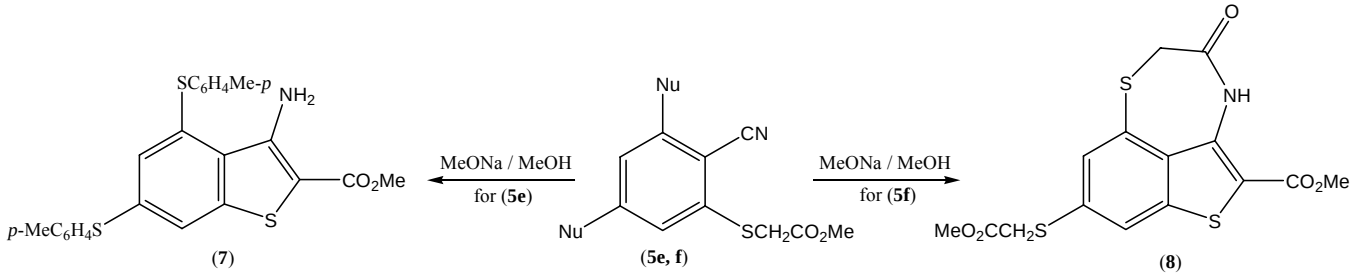
$J^{1}_{H\text{-}}{}^{19}_{F}$ with adjacent (H^5, δ 8.10 ppm) and remote (H^3, δ 8.17 ppm) protons are 10.0 Hz and < 2.0 Hz, respectively. The observed regioselectivity is in agreement with the reported ortho-selectivity of nucleophilic substitution reactions in 1-R-2,4-dinitro- and 1-R-2,4,6-trinitrobenzens.[9,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

The results of substitution reaction are affected by the nature of both a nucleophile and a solvent. Reactions of the nitrile (**4b**) with HSC_6H_4Me-4 / K_2CO_3 and $HSCH_2CO_2Me$ / K_2CO_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 α-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**.[18]



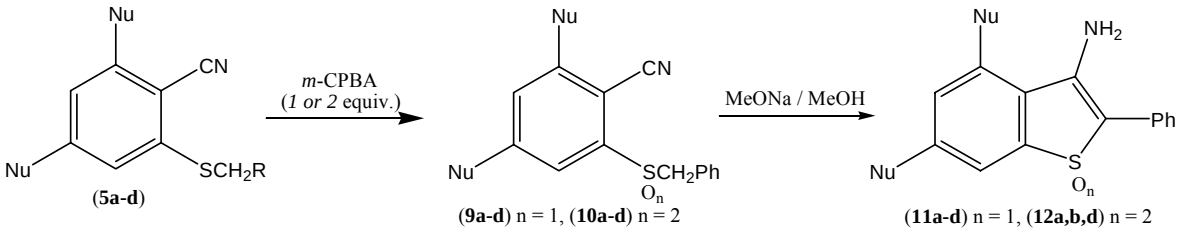
Scheme 2

Substituted benzonitriles (**5a-f**) were found to be convenient building blocks for the synthesis of nitro-free bezothiophene 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(methoxycarbonyl-methylthio)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,[16–20] synthesis of nitro-free heterocycles remains a major challenge.[21] 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.[12, 14]

EXPERIMENTAL

^{1}H, and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz {^{1}H}) and a Bruker DRX-500 spectrometer (500.13 MHz {^{1}H}, 125.76 MHz {^{13}C}) in DMSO-d_6. Chemical shifts of ^{1}H were measured relative to Me_4Si as the internal standard, ^{13}C – relative to DMSO-d_6. MS spectra were recorded on a MS-30 (Kratos) instrument (EI). TLC was performed on Silpearl UV-250 silica gel. The compounds (**1**)[22] (**2**), (**3a,b**)[12, 14] were synthesized according to the literature procedures. Solvents were purified by standard methods.

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

$POCl_3$ (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. ^{1}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 $C_{14}H_9N_3O_4S$: 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 $POCl_3$ (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. ^{1}H NMR: δ 3.75 (s, 3H); 4.39 (s, 2H); 8.65 (s, 1H); 8.68 (s, 1H). *Anal*. Calcd for $C_{10}H_7N_3O_6S$: 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. ^{1}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). ^{13}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^+, 68%), 270 (3%), 256 (7%), 194 (7%), 150 (10%), 91 (100%). *Anal*. Calcd for $C_{16}H_{15}NO_2S$: 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_2CO_3 (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_4 (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. ^{1}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). ^{13}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^+, 30%), 318 (15%), 91 (100%). *Anal*. Calcd for $C_{26}H_{19}NO_2S$: 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_2CO_3 (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}H NMR: δ 4.34 (s, 2H); 4.72 (q, J_{H-F} = 8.0 Hz, 2H); 4.76 (q, J_{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 (M^+, 15%), 330 (3%), 309 (4%), 266 (4%), 91 (100%). *Anal*. Calcd for $C_{18}H_{13}NO_2F_6S$: 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)

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°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 acetone - *i*-PrOH mixture to give **5d**. Yield 1.17 g (95%), mp 119-120°C. ^{1}H NMR: δ 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 $C_{14}H_9N_7S$: 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 K_2CO_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°C for 5 h, cooled to 20°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 135-137°C. ^{1}H NMR: δ 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 $C_{24}H_{21}NO_2S_3$: 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 α-mercaptoacetate (0.13 mL, 0.15 g, 1.43 mmol) and K_2CO_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°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 85-86°C (lit.,[12] mp 84-86°C). ^{1}H NMR: δ 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 α-mercaptoacetate (1.60 g, 15.3 mmol) and K_2CO_3 (2.12 g, 15.3 mmol) in DMF following the procedure and experimental conditions described in the literature.[12]

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 122-125°C. ^{1}H NMR: δ 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_{H-F} = 10 Hz, 1H); 8.17 (s, 1H). MS (*m/z*, I): 288 (M^+, 5%), 197 (2%), 91 (100%). *Anal*. Calcd for

$C_{14}H_9N_2O_2FS$: 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.,[13] mp 196-198°C). ^{1}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_2CO_3 (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. ^{1}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 $C_{24}H_{21}NO_2S_3$: 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)benzonitrile (**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. ^{1}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). ^{13}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^+, 100%), 350 (20%), 323 (25%). *Anal*. Calcd for $C_{15}H_{13}NO_5S_3$: 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)benzonitriles (9a-d) and 4,6-disubstituted 2-(benzylsulfonyl)benzonitriles (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_2Cl_2 (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

$NaHCO_3$ water solution. The aqueous layer was separated, extracted with CH_2Cl_2 (5 mL) and discarded. Combined organic layers were dried over anhydrous $MgSO_4$ 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. ^{1}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). ^{13}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^+, 10%), 285 (2%), 210 (5%), 91 (100%). *Anal*. Calcd for $C_{16}H_{15}NO_3S$: 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. ^{1}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). ^{13}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^+, 2%), 409 (2%), 334 (2%), 317 (2%), 285 (5%), 91 (100%). *Anal*. Calcd for $C_{26}H_{19}NO_3S$: 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. ^{1}H NMR: δ 4.04 (d, *J* = 12.5 Hz, 1H); 4.33 (d, *J* = 12.5 Hz, 1H); 4.63 (m, $J_{H\text{-}H}$ =10 Hz, $J_{H\text{-}F}$ = 8.3 Hz, 1H); 4.77 (m, $J_{H\text{-}H}$ =10 Hz, $J_{H\text{-}F}$ = 8.3 Hz, 1H); 4.89 (m, $J_{H\text{-}F}$ = 8.3 Hz, 2H); 6.87 (s, 1H); 7.30 (s, 1H); 7.24 - 7.40 (m, 5H). MS (*m/z*, I): 437 (M^+, 5%), 421 (3%), 346 (15%), 331 (5%), 91 (100%). *Anal*. Calcd for $C_{18}H_{13}NO_3F_6S$: 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. ^{1}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^+, 10%), 91 (100%). *Anal*. Calcd for $C_{14}H_9N_7OS$: 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. ^{1}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). ^{13}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^+, 3%), 254 (5%), 253 (40%), 238 (8%), 210 (13%), 91 (100%). *Anal*. Calcd for $C_{16}H_{15}NO_4S$: 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}H NMR: δ 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 $C_{26}H_{19}NO_4S$: 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 (M^+, 2%), 377 (30%); 91 (100%).

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

Yield 91%, mp 132-134°C. ^{1}H NMR: δ 4.69 (s, 2H); 4.81 (q, J_{H-F} = 8.0 Hz, 2H); 4.94 (q, J_{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 (M^+, 5%), 439 (2%), 390 (14%), 389 (100%), 320 (5%), 91 (100%). *Anal*. Calcd for $C_{18}H_{13}NO_4F_6S$: 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}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). *Anal*. Calcd for $C_{14}H_9N_7O_2S$: 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}H NMR: δ 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 (M^+, 30%), 285 (25%), 224 (30%), 196 (100%), 105 (20%), 77 (45%). *Anal*. Calcd for $C_{16}H_{15}NO_3S$: 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}H NMR: δ 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 (M^+, 30%), 409 (30%), 348 (25%), 320 (100%), 105 (30%), 77 (100%). *Anal*. Calcd for $C_{26}H_{19}NO_3S$: 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}H NMR: δ 4.94 (q, J_{H-F} = 8.0 Hz, 2H); 5.13 (q, J_{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}C NMR: δ 65.3 (q, $^2J_{C-F}$ = 33.9 Hz), 104.7, 106.5, 109.9, 115.5, 123.7 (q, $^1J_{C-F}$ = 277.9 Hz), 125.8,

127.3, 128.9, 132.4, 143.2, 148.1, 153.4, 159.1. *Anal*. Calcd for $C_{18}H_{13}NO_3F_6S$: 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. ^{1}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^+, 30%), 307 (10%), 266 (5%), 251 (10%), 238 (10%), 218 (5%), 105 (100%), 77 (80%). *Anal*. Calcd for $C_{14}H_9N_7OS$: 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. ^{1}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 $C_{16}H_{15}NO_4S$: 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. ^{1}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^+, 60%), 409 (10%), 336 (15%), 319 (15%), 105 (40%), 77 (100%). *Anal*. Calcd for $C_{26}H_{19}NO_4S$: 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. ^{1}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 $C_{14}H_9N_7O_2S$: 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.

REFERENCES

1. D. M. Berger, M. D. Dutia, F. F. Demorin, D. H. Boschelli, D. W. Powell, H. Tsou, A. Wissner, N. Y. Zhang, and B. Wu, PCT Int. Appl. WO 01 47,892 (Cl. C07D 215/54) 5 July 2001. (*Chem. Abstr.*, 135, 92639x).
2. K. Gorlitzer, C. Kramer, and Ch. Boyle, *Pharmazie*, 2000, **55**, 595.

3. M. D. Meyer, R. J. Altenbach, F. Z. Basha, W. A. Carroll, S. Condon, S. W. Elmore, J. F. Kewin, K. B. Sippy, K. Teitje, M. D. Wendt, A. A. Hancock, M. E. Brune, S. A. Buckner, and I. Drizin, *J. Med. Chem.*, 2000, **43**, 1586.
4. J. R. McCowan, D. J. Sall, and J. E. Toth, Eur. Pat. Appl. EP 997,460 (Cl. C07D 333/66) 3 May 2000 (*Chem. Abstr*., 132, 308240y).
5. H. D. H. Showalter, A. J. Bridges, H. Zhou, A. D. Sercel, A. McMichael, and D. W. Fry, *J. Med. Chem.*, 1999, **42**, 5464.
6. A. Martinez, A. Castro, C. Gil, M. Miralpeix, V. Segarra, T. Domenech, J. Beleta, J. M. Palacios, H. Ryder, X. Miro, C. Bonet, J. M. Casacuberta, F. Azorin, B. Pina, and P. Puigdomenech, *J. Med. Chem.*, 2000, **43**, 683.
7. M. Tokano, Sh. Kawamura, and T. Komori, PCT Int. Appl. WO 00 15,633 (Cl. C07D 405/04) 23 May 2000 (*Chem. Abstr.*, 132, 222545q).
8. K. Gorlitzer and C. Kramer, *Pharmazie*, 2000, **55**, 645.
9. J. R. Beck, *J. Org. Chem.*, 1972, **37**, 3224.
10. J. R. Beck and J. A. Yahner, *J. Org. Chem.*, 1974, **39**, 3440.
11. J. R. Beck, *J. Heterocycl. Chem.*, 1978, **15**, 513.
12. S. G. Zlotin, P. G. Kislitsin, A. V. Samet, E. A. Serebryakov, L. D. Konyushkin, V. V. Semenov, A. C. Buchanan III, and A. A. Gakh, *J. Org. Chem.*, 2000, **65**, 8430.
13. I. L. Dalinger, T. I. Cherkasova, S. S. Vorob'ev, A. V. Alexandrov, G. P. Popova, and S. A. Shevelev, *Russ. Chem. Bull.*, 2001, **50**, 2401.
14. A. I. Gerasyuto, S. G. Zlotin, and V. V. Semenov, *Synthesis*, 2001, 300.
15. A. S. Bailey, B. R. Henn, and J. M. Langdon, *Tetrahedron*, 1963, **19**, 161.
16. S. G. Zlotin, P. G. Kislitsin, A. I. Podgursky, A. V. Samet, V. V. Semenov, A. C. Buchanan III, and A. A. Gakh, *J. Org. Chem.*, 2000, **65**, 8439.
17. E. A. Serebryakov, P. G. Kislitsin, V. V. Semenov, and S. G. Zlotin, *Synthesis*, 2001, 1659.
18. S. A. Shevelev, I. L. Dalinger, and T. I. Cherkasova, *Tetrahedron Lett.*, 2001, **42**, 8539.
19. V. V. Rozhkov, A. M. Kuvshinov, and S. A. Shevelev, *Org. Prep. Proc. Int.*, 2000, **32**, 94.
20. V. V. Rozhkov, A. M. Kuvshinov, V. I. Gulevskaya, I. I. Chervin, and S. A. Shevelev, *Synthesis*, 1999, 2065.
21. A. V. Samet, V. N. Marshalkin, K. A. Kislyi, N. B. Cherhysheva, Yu. A. Strelenko, and V. V. Semenov, *J. Org. Chem.*, 2005, **70**, 9371.
22. J. Konarsky and A. Graczyk, *Rocz. Chem.*, 1972, **46**, 745.