Tetrahedron 66 (2010) 2474–2485

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A convenient approach towards 2- and 3-aminobenzo[*b*]thiophenes

Dmitry A. Androsov [a,b,*], Andrey Y. Solovyev [b], Mikhail L. Petrov [a], Ray J. Butcher [c], Jerry P. Jasinski [d]

[a] *Department of Organic Chemistry, Saint-Petersburg State Institute of Technology, Moskovskii prospekt 26, Saint-Petersburg 190013, Russian Federation*
[b] *Center for Photochemical Sciences, Bowling Green State University, Bowling Green, OH 43403, USA*
[c] *Department of Chemistry, Howard University, Washington, DC 20059, USA*
[d] *Department of Chemistry, Keene State College, Keene, NH 03435, USA*

ARTICLE INFO

Article history:
Received 21 October 2009
Received in revised form 10 December 2009
Accepted 18 January 2010
Available online 1 February 2010

ABSTRACT

Reaction of 1-(2-chloro-5-nitrophenyl)ethanone via Willgerodt–Kindler route with primary or secondary amines and sulfur allows a simple, efficient one-pot synthesis of 3-aminobenzo[*b*]thiophenes. Base-catalyzed transformation of 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole in the presence of primary and secondary amines offers a convenient approach towards 2-aminobenzo[*b*]thiophenes.

1. Introduction

Though derivatives of 2-dimethylamino-6-hydroxybenzo[*b*]thiophene are important intermediates in the synthesis of the selective estrogen receptor modulators—raloxifene and its analogs,[1–4] 2-aminobenzo[*b*]thiophenes in general belong to an elusive group of benzo[*b*]thiophenes.

It was found that some 3-aminobenzo[*b*]thiophenes exhibit high antifungal activity against clinically relevant *Candida*, Aspergillus, and *dermatophyte* species. The most active compound *N*-(benzo[*b*]thiophen-3-yl)pyridin-3-amine showed a broad spectrum of activity against all tested fungal strains, including fluconazole-resistant yeasts and *Aspergillus fumigatus*, especially important organisms from the clinical point of view.[5] In vitro antimicrobial activity of some 3-arylaminobenzo[*b*]thiophenes was evaluated. Selectivity against *Bacillus cereus* was observed, with low minimal inhibitory concentrations.[6]

2-Aminobenzo[*b*]thiophene itself can be obtained in five steps (overall yield 48%) from thiosalicylic acid. The key reaction involves thio-ether cleavage of *ortho*-benzylmercaptophenylacetonitrile. In contrast to 2-hydroxybenzo[*b*]thiophene, which exists mainly as the tautomeric keto form, 2-aminobenzo[*b*]thiophene exists preferably in the amino form.[7] Other 2-aminobenzo[*b*]thiophenes, synthesized classically, include 2-morpholinobenzo[*b*]thiophene, which was obtained by the addition of morpholine and its alkali metal salt to the C^2–C^3 double bond of benzo[*b*]thiophene (yield 45%) followed by aromatization with sulfur at 250 °C (yield 60%),[8] 2-piperidino benzo[*b*]thiophene prepared in 85% yield by heating a mixture of 2-bromobenzo[*b*]thiophene and piperidine in a sealed tube at 220 °C for 28 h and in 20% yield by heating a mixture of 3-bromobenzo[*b*]thiophene and piperidine in a sealed tube at 250–260 °C for 46 h,[9] and hydrogenation of 2-(phenylazo)-3,4,6-trimethylbenzo[*b*]thiophene in the presence of acetic anhydride, which afforded 2-acetamido-3,4,6-trimethylbenzo[*b*]thiophene (yield 18%).[10] 2-Dimethylamino-6-benzyloxybenzo[*b*]thiophene was prepared in two steps by the treatment of a mixture of 4-benzyloxybenzaldehyde and *N*,*N*-dimethylthioformamide with LDA at −78 °C and following cyclization–aromatization with $MeSO_3H$.[4]

3-Dialkylaminobenzo[*b*]thiophenes were synthesized by the reaction of 3-bromobenzo[*b*]thiophene-1-oxide with secondary amines followed by reduction of 3-aminobenzo[*b*]thiophene-1-oxide with Dibal-H in a 60–80% yield.[11] A number of 3-alkyl- and 3-arylaminobenzo[*b*]thiophenes were synthesized by palladium- or copper-catalyzed amination of 3-bromobenzo[*b*]thiophene.[12–15]

3-Aminobenzo[*b*]thiophene itself was previously prepared by: (1) reduction of 3-nitrobenzo[*b*]thiophene using ethanolic ammonium sulfide (75% yield). 3-Nitrobenzo[*b*]thiophene was obtained from benzo[*b*]thiophene through the sequence of reactions involving sulfonation, nitration and desulfonation (8% overall yield),[16] (2) thermal decomposition of 3-azidobenzo[*b*]thiophene in diethyl- or dimethylamine in a sealed tube at 90 °C (6–10% yield).[17]

3-Aminobenzo[*b*]thiophenes-2-carboxylates were prepared by (a) the reaction of 3-chloro-1,2-benzothiazole with diethyl sodium malonate (70% yield), [18] (b) condensation of 2-cyanothiophenol with ethyl bromomalonate in aqueous sodium hydroxide (82% yield),[18] (c) by the reaction of 2-fluorobenzonitrile with ethyl thioglycolate and excess of triethylamine in DMSO at 100 °C (62–70% yield).[19,20]

In previous papers we have reported that 1-(2-chloro-5-nitrophenyl)ethanone can serve as a precursor for 2-aminobenzo[*b*]thiophenes,[21] while 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole, prepared from 1-(2-chloro-5-nitrophenyl)ethanone,

* Corresponding author. Tel.: +7 812 463 6477; fax: +7 812 460 8146.
E-mail address: da_androsov@hotmail.com (D.A. Androsov).

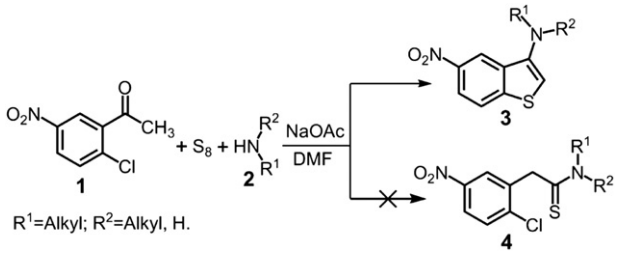
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.01.069

was a convenient precursor for indole-2-thiols.[22,23] Recently we discovered that structures reported in our original papers were incorrectly assigned. In this paper we want to summarize our previous results and to report the revised structures supported by additional spectroscopic evidences and X-ray crystallographic data.

2. Results and discussion

2.1. 3-Aminobenzo[*b*]thiophenes

The reaction of 1-(2-chloro-5-nitrophenyl)ethanone **1** with primary and secondary amines **2** under Willgerodt–Kindler conditions afforded 3-aminobenzo[*b*]thiophenes **3** (Scheme 1, Table 1).



Scheme 1.

According to the general procedure, the substrate **1** was heated in DMF at 35–100 °C in the presence of amine **2** (1.2–3.7 equiv), sulfur (1.5–5 equiv), and NaOAc (0–3 equiv) for 6–20 min. The solvent was removed under reduced pressure and the desired product was isolated by column chromatography.

A plausible mechanism of the reaction is shown below (Scheme 2). The first stage of the reaction is enamine **5** formation by the ketone group of acetophenone **1** and the amine group of alkylamine. The intermediate **5** reacts with sulfur to give the sulfide **6**. Subsequent formation of enthiolate **8**, followed by cyclization, leads to final product **3**. As for conventional Willgerodt–Kindler reaction, the rearrangement reaction takes place when the amine group attacks thiocarbonyl **7** in a nucleophilic addition forming an aziridine ring **9** and the amine group moving along the central C–C bond rearranging to **10**, further proton exchange and tautomerization affords thioacetamide **4**.[24]

Generally, we found that a nitro group *para* to the chlorine atom promotes the reaction. Reaction did not occur in the absence of nitro group. For example, 1-(2-chlorophenyl)ethanone yielded a complex mixture of products instead of corresponding benzo[*b*]thiophene.

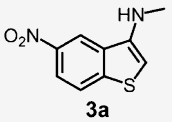
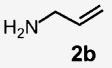
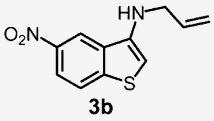
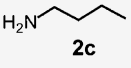
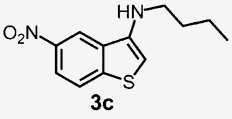
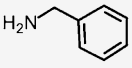
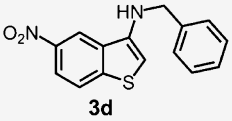
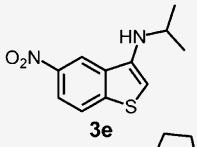
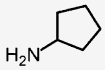
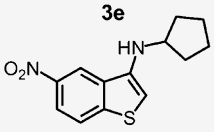
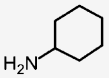
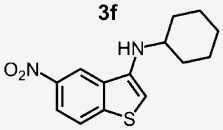
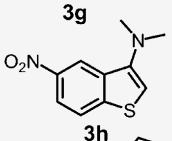
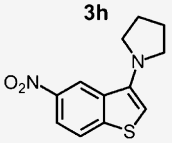
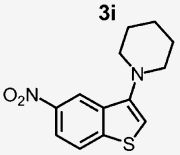
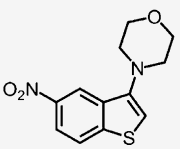
The nature of base is not important. K_3PO_4, NaOAc or an excess of amine can serve as a base. Primary amines gave better yields of 3-aminobenzo[*b*]thiophenes than secondary amines.

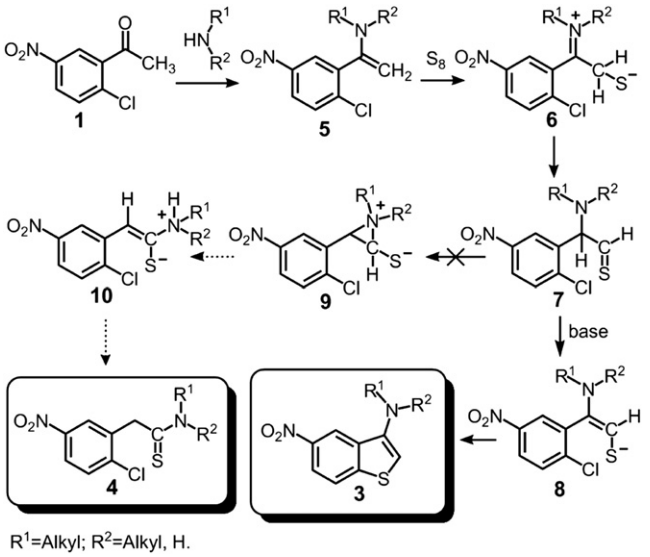
The reaction crucially depends on the concentration of the amine. A 1.5–3 fold excess was preferable for secondary amines and a 1.5–2 fold excess was preferable for primary amines. The content of by-products depends on the nature of amine. In case of primary amines, the major by-product was 3-methyl-5-nitrobenzo[*d*]isothiazole, becoming dominant in the presence of 8–10 fold excess of amine. In contrast, in the case of secondary amines the main by-product was the product of nucleophilic substitution on the benzene ring.

We also found that the optimal ratio of acetophenone/sulfur is 1:5. The better yields of primary amines were observed at lower temperature (35–60 °C) while higher temperature (60–100 °C) worked better for secondary amines (Table 2). DMF was found to be the most favorable solvent. Whereas primary amines are usually more reactive than secondary amines in the classical Willgerodt–Kindler reaction.[25]

Steric effects play an important role. The yield of 2-cyclopentylaminobenzo[*b*]thiophene **3f** (40%, entry **6**) was higher than

Table 1
Synthesis of 3-aminobenzo[*b*]thiophenes

Entry	Amine	Product	Yield (%)
1	 **2a**	 **3a**	46
2	 **2b**	 **3b**	47
3	 **2c**	 **3c**	36
4	 **2d**	 **3d**	30
5	 **2e**	 **3e**	14
6	 **2f**	 **3f**	40
7	 **2g**	 **3g**	19
8	 **2h**	 **3h**	4
9	 **2i**	 **3i**	31
10	 **2j**	 **3j**	10
11	 **2k**	 **3k**	12

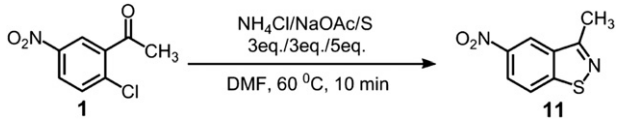


Scheme 2.

Table 2
Conditions for preparation of 3-aminobenzo[*b*]thiophenes

Entry	Product	Ratio Amine/S/Base	Temperature (°C)	Time (min)
1	**3a**	3/5/3	60	10
2	**3b**	2.17/5/0	45	10
3	**3c**	3.2/3/2	60	8
4	**3d**	3.8/5/0	60	10
5	**3e**	2.3/5/0	60	10
6	**3f**	2.15/5/0	60	10
7	**3g**	1.95/5/0	35	6
8	**3h**	1.5/1.5/1.5	100	180
9	**3i**	3.7/3/2	60	15
10	**3j**	1.2/1.5/1.5	100	20
11	**3k**	1.4/5/1.5	100	12

the yield of 2-cyclohexylaminobenzo[*b*]thiophene **3g** (19%, entry **7**). Sterically hindered (dibutylamine, diallylamine, di-*iso*-propylamine), aromatic (aniline) and heterocyclic (benzotriazole) amines failed to react. An attempt to obtain *N*-unsubstituted benzothiophene using NH_4Cl in the presence of NaOAc afforded 3-methyl-5-nitro-benzo[*d*]isothiazole **11**, yield 78% (Scheme 3). The synthesis of **11** under harsh conditions is reported in literature.[26]

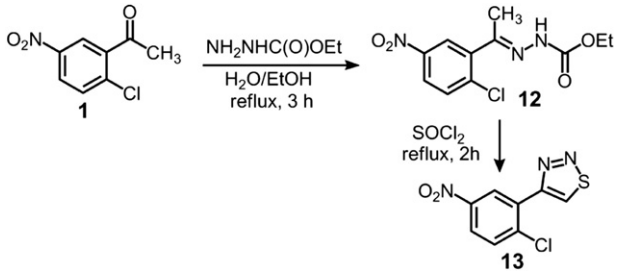


Scheme 3.

Whereas the classical Willgerodt–Kindler reaction requires high temperature and prolonged heating,[27,28] microwave assistance[25,29–31] or special reagents,[32] surprisingly, our reaction proceeded under mild conditions (Table 2).

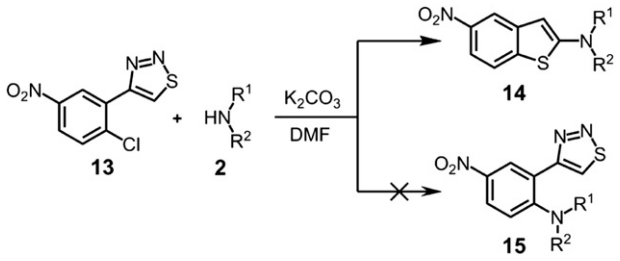
2.2. 2-Aminobenzo[*b*]thiophenes

The Hurd–Mori reaction allows synthesis of 4-substituted 1,2,3-thiadiazoles from methyl ketones by the action of thionyl chloride on the corresponding ethylcarbazones or tosylhydrazones.[33,34] This procedure was applied to the synthesis of earlier unknown 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole **13** from 1-(2-chloro-5-nitrophenyl)-ethanone **1** in 89% overall yield (Scheme 4).



Scheme 4.

We next conducted the base-catalyzed (K_2CO_3) alkylamination of **13** with a variety of primary and secondary amines **2a**–**x** in DMF at moderate temperature (50–90 °C). The products of the reaction were unexpected 2-aminobenzo[*b*]thiophenes **14a**–**x** (Scheme 5, Tables 3 and 4). In addition, we found that the reaction is tolerant to the medium and MeCN, Me_2CO, MeOH, EtOH can be used as the solvents. The use of DMF allows the reaction even at room temperature (20–25 °C).

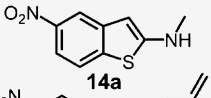
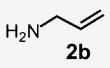
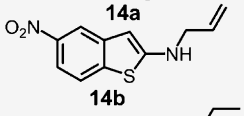
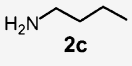
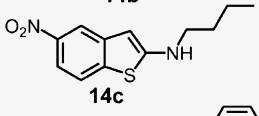
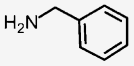
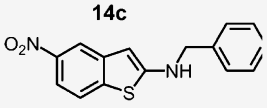
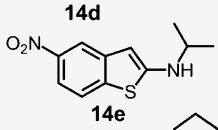
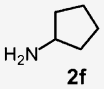
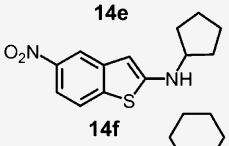
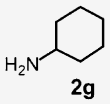
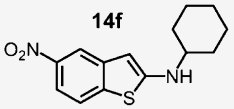
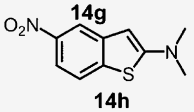
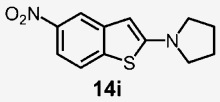
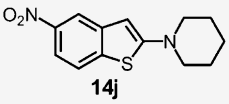
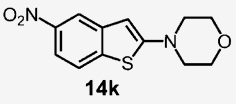
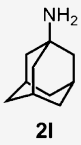
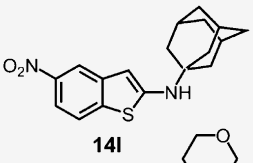
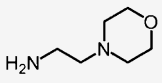
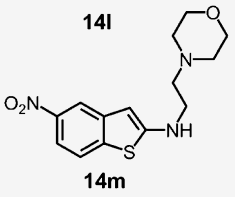
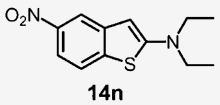
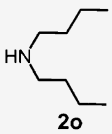
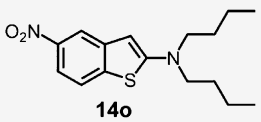


Scheme 5.

Generally, we did not optimize the reaction conditions (ratio of reagents, choice of solvent, temperature) in each particular case. But according to our observations the yield of 2-aminobenzo[*b*]thiophene can be increased at lower reaction temperature (92%, 22 h; 25 °C) vs (44%—3 h; 50 °C) for product **14c**. Reaction of **13** with aniline and *N*-phenylhydrazine under the same conditions gave none of the desired 2-aminobenzo[*b*]thiophene.

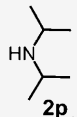
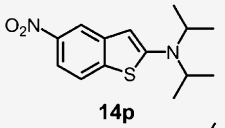
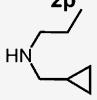
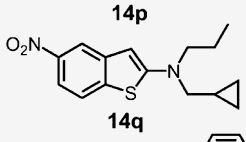
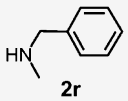
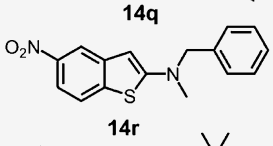
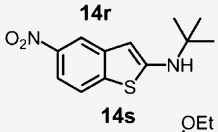
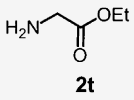
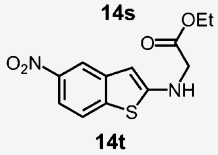
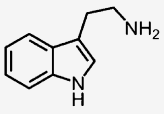
The mechanism of this reaction was studied by ^1H NMR monitoring of a reaction mixture containing **13**, **2c**, and K_2CO_3 in DMF at 25 °C (Scheme 6). Initially, the thiadiazole ring-opening was indicated by the disappearance of the thiadiazole H5 at δ_H 9.19. Decomposition of the electron-withdrawing thiadiazole ring was accompanied by nitrogen evolution and formation of thioamide **20**. The appearance of N*H* at δ_H 7.44 and an upfield shift of phenyl protons at the 3, 4, and 6 positions moved by 0.30, 0.16, and 0.89 ppm, respectively, were observed. We also followed the progress of the reaction by GC–MS. This supports formation of intermediate **20** (*m*/*z* 286). After 22 h the transformation was complete and the NMR spectrum showed a clean absorption pattern of *N*-butyl-5-nitrobenzo[*b*]thiophen-2-amine **14c** with δ_H 0.97 ($CH_3CH_2CH_2CH_2$–NH), 1.46 ($CH_3CH_2CH_2CH_2$–NH), 1.67 ($CH_3CH_2CH_2CH_2$–NH), 3.24 ($CH_3CH_2CH_2CH_2$–NH), 4.28 ($CH_3CH_2CH_2CH_2$–N*H*), 6.12 (H3), 7.59 (H7), 7.87 (H6), 8.21 (H4). There were no detectable impurities present. The supposed intermediates **16**, **17**, **18**, **19**, **21** were not detected by ^1H NMR but their formation is not in conflict with our observations and data documented in literature.[35–37]

Table 3
Synthesis of 2-aminobenzo[*b*]thiophenes

Entry	Amine	Product	Yield (%)
1	 **2a**	 **14a**	6
2	 **2b**	 **14b**	42
3	 **2c**	 **14c**	44
4	 **2d**	 **14d**	33
5	 **2e**	 **14e**	29
6	 **2f**	 **14f**	33
7	 **2g**	 **14g**	38
8	NH_4OAc	 **14h**	75
9	 **2i**	 **14i**	7
10	 **2j**	 **14j**	17
11	 **2k**	 **14k**	49
12	 **2l**	 **14l**	26
13	 **2m**	 **14m**	61
14	 **2n**	 **14n**	55
15	 **2o**	 **14o**	33

(*continued on next page*)

Table 3 (*continued*)

Entry	Amine	Product	Yield (%)
16	 **2p**	 **14p**	25
17	 **2q**	 **14q**	38
18	 **2r**	 **14r**	41
19	 **2s**	 **14s**	39
20	 **2t**	 **14t**	9
21	 **2u**	**14u**	23
22	**2v**	**14v**	63
23	**2w**	**14w**	20
24	**2x**	**14x**	74

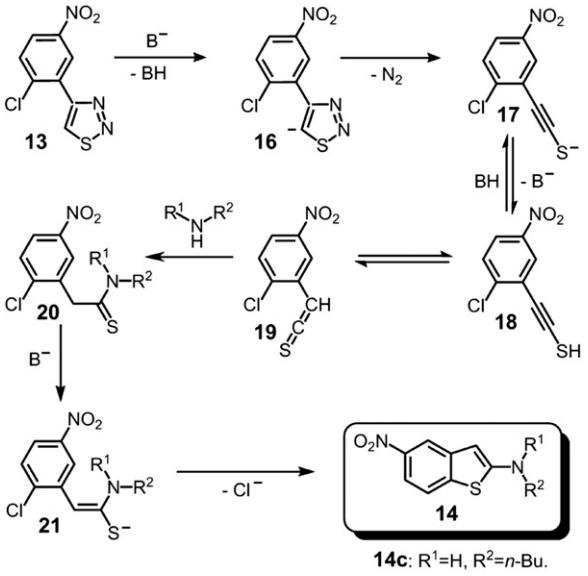
Compound **14i** (entry 9) was obtained in a low yield (7%) due to the relatively high nucleophilicity of the pyrrolidine, which displaces the chlorine atom on the benzene ring faster than cyclization to **14i** occurs, affording thioamide **22** (62%) as a major product (Scheme 7).

It is noteworthy that the best result in the synthesis of compound **14h** (entry 8) was achieved using the combination NH_4OAc/K_2CO_3/DMF that made it possible to generate dimethylamine in situ (Scheme 8).

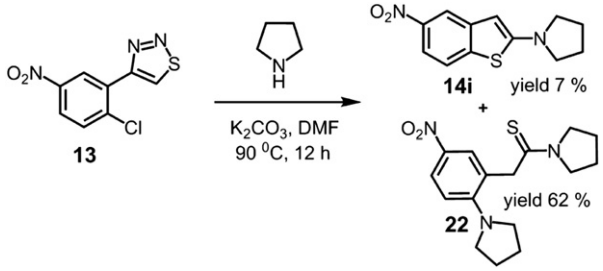
In order to understand how the electron-withdrawing nitro group affects the reaction we prepared 4-(2-chlorophenyl)-1,2,3-thiadiazole **25** (overall yield 37%) from 1-(2-chlorophenyl)-ethanone **23** according to the Hurd–Mori procedure.[34] Compound **25** was heated in the presence of *n*-$BuNH_2$ and K_2CO_3 at 70 °C for 24 h but only starting material **25** and thioamide **26** were detected in the reaction mixture. Complete conversion of **25** to **26** was achieved at elevated temperature (130 °C), but no traces of cyclic product **27** were found. Thus, the presence of the activating nitro group on the

Table 4
Conditions for preparation of 2-aminobenzo[6]thiophenes

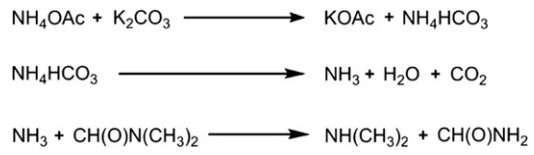
Entry	Product	Ratio 13/2/K_2CO_3	Temperature (°C)	Time (h)
1	**14a**	1/3/2	60	6
2	**14b**	1/3/2	70	3
3	**14c**	1/3/2	50	3
4	**14d**	1/3/2	70	3
5	**14e**	1/4/2	60	6
6	**14f**	1/3/2	70	3
7	**14g**	1/3/2	70	3
8	**14h**	1/5/7	90	12
9	**141**	1/5/5	90	12
10	**14j**	1/5/5	90	12
11	**14k**	1/5/5	90	12
12	**14l**	1/3/2	80	9
13	**14m**	1/3/2	80	3
14	**14n**	1/5/3	90	12
15	**14o**	1/5/3	90	12
16	**14p**	1/5/5	90	12
17	**14q**	1/5/5	90	12
18	**14r**	1/3/3	90	12
19	**14s**	1/3/2	70	3
20	**14t**	1/1.05/3	80	3
21	**14u**	1/2/2	70	3
22	**14v**	1/3/3	90	12
23	**14w**	1/3/3	90	12
24	**14x**	1/3/3	90	12



Scheme 6.

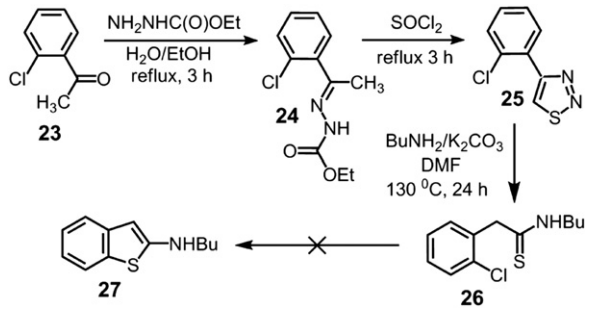


Scheme 7.



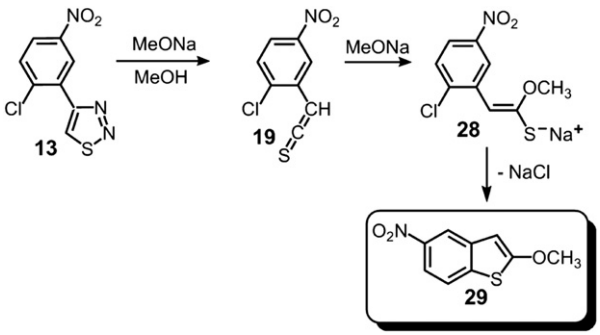
Scheme 8.

phenyl ring makes 1,2,3-thiadiazole ring susceptible to proton abstraction facilitating anionic ring-opening. In addition, cyclization of **26** to **27** does not occur since the chlorine atom is insensitive to intramolecular nucleophilic attack by sulfur under the reaction conditions (Scheme 9).



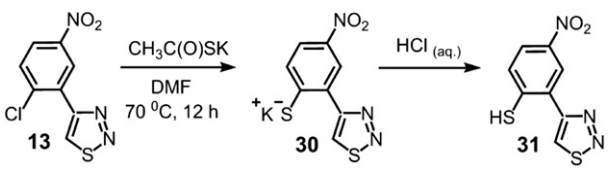
Scheme 9.

Treatment of **13** with MeONa in MeOH under an inert atmosphere led to 2-methoxy-5-nitrobenzo[*b*]thiophene **29** (yield 23%). Formation of **29** can be explained relying on already known data on the reactivity of 5-unsubstituted 1,2,3-thiadiazoles.[35–37] By analogy with Scheme 6, an addition of MeONa to thioketene **19** results in enthiol anion **28** cyclizing to benzothiophene **29** (Scheme 10).



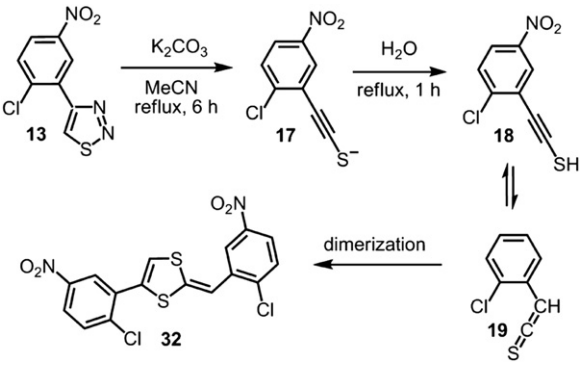
Scheme 10.

An attempt to introduce the sulfur-containing nucleophile by reaction of **13** with potassium thioacetate resulted in the product of nucleophilic substitution on the benzene ring. This gave thiophenolate **30** without decomposition of the heterocyclic ring. Anion **30** can be trapped as thiol **31** (yield 80%) after addition of diluted HCl (Scheme 11).



Scheme 11.

Decomposition of **13** under influence of base (K_2CO_3, MeCN; 80 °C, 6 h) in the absence of nucleophiles afforded alkynethiolate **17**, which reacted with water forming alkyne thiol **18**. Tautomerization of **18** to **19** and subsequent dimerization afforded dithiafulvene **32** (Scheme 12).

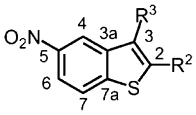


Scheme 12.

2.3. Effect of substitution pattern on ^{1}H NMR chemical shifts in 2- and 3-aminobenzo[*b*]thiophenes

In the ^{1}H NMR spectra of 2- and 3-aminobenzo[*b*]thiophenes the position of H3 and H2 protons is an indicative of the degree of overlap between electron pair on the amino group nitrogen atom and the *endo*-cyclic C2–C3 double bond. In contrast to electron-deficient 5-nitrobenzo[*b*]thiophene,[38] the heterocyclic ring in 2- and 3-aminobenzo[*b*]thiophenes is electron-rich due to the donating nature of the amino group. This results in a significant shielding of proton in *ortho*-position to the amino group (Table 5).

Table 5
Chemical shifts (δ, ppm) of ring protons in 2- and 3-aminobenzo[*b*]thiophenes ($CDCl_3$)



Entry	Compd	R^2	R^3	δ_{H2}	δ_{H3}	δ_{H4}	δ_{H6}	δ_{H7}
1	—	H	H	7.65	7.49	8.71	8.18	7.98
2	**3a**	H	NHMe	6.16	—	8.48	8.16	7.84
3	**3h**	H	$N(Me)_2$	6.68	—	8.73	8.19	7.88
4	**3i**	H		6.20	—	8.87	8.12	7.82
5	**3j**	H		6.74	—	8.62	8.17	7.87
6	**14a**	NHMe	H	—	6.13	8.24	7.89	7.60
7	**14h**	$N(Me)_2$	H	—	5.97	8.20	7.82	7.59
8	**14i**		H	—	5.89	8.21	7.81	7.60
9	**14j**		H	—	6.18	8.23	7.87	7.62
10	**29**	OMe	H	—	6.46	8.40	8.04	7.70

The protons on the benzene ring in 2-amino-substituted derivatives are shifted upfield comparing to the corresponding protons in isomeric 3-amino-substituted derivatives. This can be explained by the less efficient delocalization of the amino group lone-pair electrons into the benzene ring in the second case (Fig. 1, Table 6).

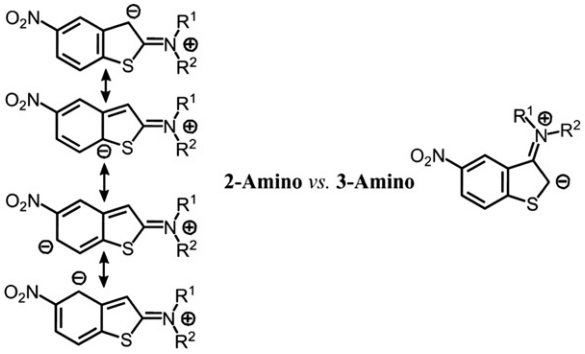


Figure 1. n_N–π_{Ar} Delocalization in 2- and 3-aminobenzo[*b*]thiophenes.

The H2 proton in *N*-methyl-5-nitrobenzo[*b*]thiophen-3-amine **3a** is shielded better ($\Delta\delta_{H2}$=+1.49 ppm) than H3 proton in isomeric *N*-methyl-5-nitrobenzo[*b*]thiophen-2-amine **14a** ($\Delta\delta_{H3}$=+1.36 ppm). Whereas H3 protons in tertiary 2-*N*,*N*-dimethylamino-, 2-pyrrolidino- and 2-piperidinobenzo[*b*]thiophenes **14h–j** ($\Delta\delta_{H3}$=+1.52, 1.60, 1.31 ppm) are shielded better than H2 proton in isomeric 3-*N*,*N*-dimethylamino-, 3-pyrrolidino- and 3-piperidino-derivatives **3h–j** ($\Delta\delta_{H2}$=+0.97, 1.45, 0.91 ppm), see Table 6.

The difference in shieldings between tertiary 2- and 3-aminobenzo[*b*]thiophenes reflects the partial deconjugation of the amino group of the latter. This effect, pronounced for sterically bulky piperidine substituent vs more compact pyrrolidine substituent, indicates the twisting of the bulky group out of conjugation due to the additional steric repulsion provoked by H4 atom in *peri*-position of the benzene ring. The similar substituent influence can be seen in ^{13}C NMR spectra of 3-aminobenzo[*b*]thiophenes: C2-atom of 3-pyrrolidino-derivative **3i** bears the larger negative charge (δ_{C2}=99.9 ppm) vs relatively positively charged C2-atom of 3-piperidino-derivative **3j** (δ_{C3}=109.7 ppm), see Table 7.

The values of the substituent-induced upfield chemical shifts of H2 and H3 atoms in aminobenzo[*b*]thiophenes are closer to those of the enamines of cyclopentanone than to the related chemical shifts in anilines (Fig. 2).[39,40]

In spite of close similarity between the NMR spectra of 2- and 3-aminobenzo[*b*]thiophenes these isomers can easily be distinguished by NOE experiment. Thus, irradiation of H3 proton in 2-amino-derivative results in a significant NOE on benzene ring H4 proton, whereas irradiation of H2 proton does not lead to perceptible NOE on H4 proton (Fig. 3).

2.4. Molecular structures of representative compounds

Biaryl system of 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole **13** has a propeller-like shape φ (C1–C6–C7–C8)=39.5° (Fig. 4).

Piperidine ring in 1-(5-nitrobenzo[*b*]thiophen-2-yl)piperidine **14j** has a shape of chair with the aromatic fragment in an equatorial position. This relatively rigid conformation prevents *N*-atom from adopting favorable sp^2 hybridization: φ (C2–C1–N2–C13)=16.5°, φ (C2–C1–N2–C9)=158.2°, and C1–N2 bond is slightly bent beyond the aromatic ring plane φ (C3–C2–C1–N2)=174.2°. The nitro group is twisted out of the benzene ring plane to a certain extent φ (C6–C5–N1–O1)=10.1° (Fig. 5).

The state of hybridization of the *N*-atom can be roughly estimated following trimethylamine example: the C–N–C angle in tetrahedral sp^3 hybridized $N(CH_3)_3$ is 108° and the total sum of

Table 6
Substituent effects on ring protons in 2- and 3-aminobenzo[*b*]thiophenes ($CDCl_3$)

Entry	Compd	R^2	R^3	δ_{H2}	δ_{H3}	δ_{H4}	δ_{H6}	δ_{H7}
1	—	H	H	0	0	0	0	0
2	**3a**	H	NHMe	+1.49	—	+0.23	+0.02	+0.14
3	**3h**	H	$N(Me)_2$	+0.97	—	−0.02	−0.01	+0.10
4	**3i**	H		+1.45	—	−0.06	+0.06	+0.16
5	**3j**	H		+0.91	—	+0.09	+0.01	+0.11
6	**14a**	NHMe	H	—	+1.36	+0.47	+0.29	+0.38
7	**14h**	$N(Me)_2$	H	—	+1.52	+0.51	+0.36	+0.39
8	**14i**		H	—	+1.60	+0.50	+0.37	+0.38
9	**14j**		H	—	+1.31	+0.48	+0.31	+0.36
10	**29**	OMe	H	—	+1.03	+0.31	+0.14	+0.28

Substituent-induced chemical shifts (Δδ, ppm). Positive values denote an upfield shift with respect to the unsubstituted substance.

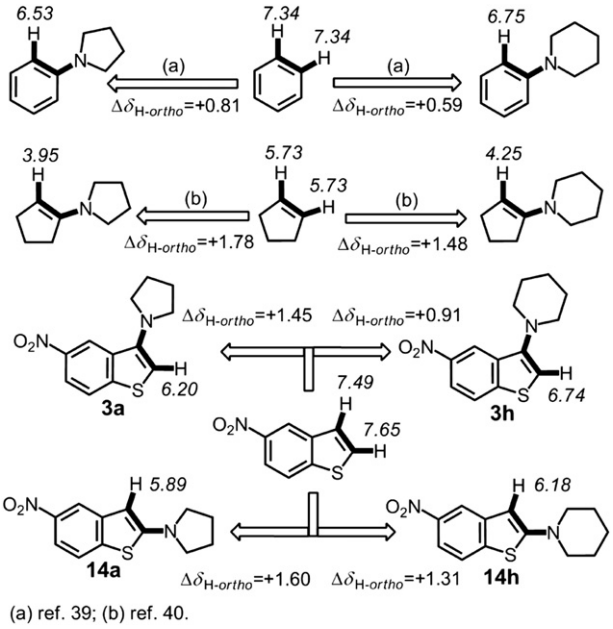
Table 7
Chemical shifts (δ, ppm) of ring carbons in 2- and 3-aminobenzo[*b*]thiophenes ($CDC1_3$)

Entry	Compd	R^2	R^3	Δ_{c2}	Δ_{c3}	Δ_{c3a}
1	**3a**	H	NHMe	97.0	145.5	132.4
2	**3h**	H	$N(Me)_2$	108.4	149.0	134.7
3	**3i**	H		99.9	145.8	133.7
4	**3j**	H		109.7	149.2	135.0
5	**14a**	NHMe	H	157.3	95.9	138.2
6	**14h**	$N(Me)_2$	H	159.9	95.5	138.3
7	**14i**		H	156.1	93.6	137.9
8	**14j**		H	160.7	97.3	138.5
9	**29**	OMe	H	168.1	98.3	138.2

C–N–C angles is 324°. The projection of the $N(CH_3)_3$ molecule on the plane gives the planar sp^2 hybridized structure and the sum of C–N–C angles amounts to 360°. The other transition states of the molecule have the sum of the C–N–C angles ranging from 324° to 360°. The sum of the R^x–N–R^y angles in the tertiary amine **14j** is 348.5°, while the corresponding value for the secondary amine **3d** is 356.4°, indicating that *N*-atom of **3d** is sp^2 hybridized to a great extent (Fig. 6).

3. Conclusion

In conclusion, we have found and developed simple, convenient approach to potentially important 3-aminobenzo[*b*]thiophenes **3** starting from cheap, commercially available 1-(2-chloro-5-nitrophenyl)ethanone **1**. The method allowed us to synthesize a number of earlier unknown heterocycles. We have also synthesized and



(a) ref. 39; (b) ref. 40.

Figure 2. Chemical shifts of protons (δ, ppm) in *ortho*-position to *N*-substituent in selected 2- and 3-aminobenzo[*b*]thiophenes, enamines of cyclopentanone, dialkylanilines and their parent compound ($CDCl_3$).

studied the reactivity of 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole **13** with *N*,*O*,*S*-nucleophiles. The unusual base-induced transformation of **13** in the presence of amines granted a simple and practical route to potentially important 2-aminobenzo[*b*]thiophenes **14**. A similar transformation of **13** in the presence of methanol produced 2-methoxy-5-nitrobenzo[*b*]thiophene **29**.

4. Experimental

4.1. General

Reagents. All chemicals were used as purchased. Solvents for crystallization and chromatography were technical grade. When

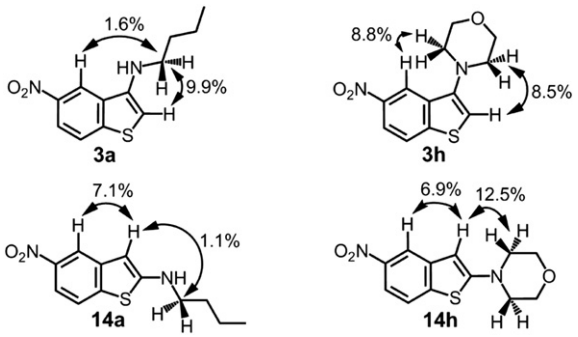


Figure 3. Selected NOE correlations for compound **3a**,**h** and **14a**,**h**.

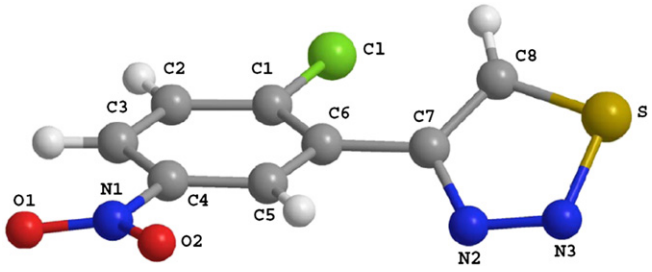


Figure 4. CHEM3D presentation of X-ray structure of 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole (**13**).

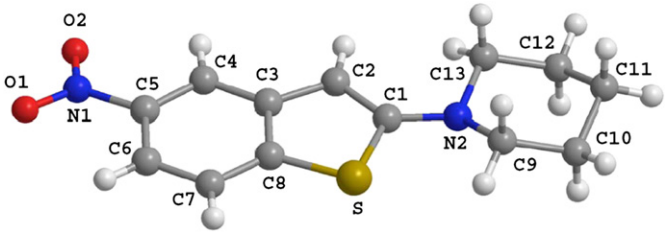


Figure 5. CHEM3D presentation of X-ray structure of 1-(5-nitrobenzo[*b*]thiophen-2-yl)piperidine (**14j**).

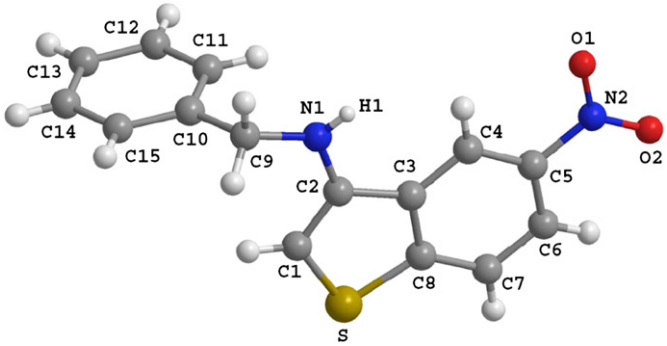


Figure 6. CHEM3D presentation of X-ray structure of *N*-benzyl-5-nitrobenzo[*b*]thiophen-3-amine (**3d**).

required, solvents were freshly distilled from appropriate drying agents before use.

General Methods. Analytical TLC was performed using silica gel 60 F_{254} TLC plates. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). Melting points were uncorrected. LR and HR mass spectra were obtained on Micromass 70-VSE and Micromass Q-Tof Ultima instruments equipped with GS, HPLC columns or by direct introduction of the effluent into the ion source using EI or ES technique. ^{1}H and ^{13}C NMR spectra (300 and 75 MHz, respectively) were recorded on a Varian Mercury Plus-300 spectrometer using TMS or the signal of residual solvent protons as an internal standard. GC analyses were performed on a Varian 3900 gas chromatograph equipped with J&W capillary column (DB-1301, 30 m×0.25 mm ID). An initial temperature of 70 °C was maintained for 3 min and then a heating rate of 20 °C/min was applied until the final temperature of 270 °C was reached.

4.2. Synthesis of 3-aminobenzo[*b*]thiophenes

*4.2.1. General procedure for the synthesis of 3-aminobenzo[b]thiophenes (**3a**–**k**).* 1-(2-Chloro-5-nitrophenyl)ethanone **1** (200 mg; 1.0 mmol), the corresponding amine **2a**–**k** (1.2–3.8 equiv), DMF (10 mL), elemental sulfur (1.5–5 equiv), and NaOAc (0–3 equiv) (in that order; for molar ratios see Table 2) were charged into 50 mL round bottom flask. The mixture was heated and stirred for 6–180 min at 35–100 °C. DMF was removed under reduced pressure and the residue purified by column chromatography (SiO_2, hexane/ethyl acetate (8:1)) affording corresponding 3-aminobenzo[*b*]thiophene **3a**–**k** (yields 4–47%, see Table 1).

*4.2.1.1. N-Methyl-5-nitrobenzo[b]thiophen-3-amine (**3a**).* Yellow solid, 96 mg (46%), mp 138–139 °C. IR (neat): 3239, 3126, 1598, 1579, 1432, 1327, 1245, 1204, 1146, 1117, 1055, 888, 843, 796, 769 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.01 (s, 3H), 4.10 (br s, 1H), 6.16 (s, 1H), 7.84 (d, J=9.0 Hz, 1H), 8.16 (dd, J=9.0, 2.4 Hz, 1H), 8.48 (d, J=2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 32.2, 97.0, 115.6, 118.8, 123.6, 132.4, 143.5, 144.7, 145.5. *m*/*z* (EI) 208 (M^+, 49%), 162 (100), 134 (44), 89 (21), 63 (30). HRMS (EI) calcd for $C_9H_8N_2O_2S$ [M^+] 208.0307, found 208.0306.

*4.2.1.2. N-Allyl-5-nitrobenzo[b]thiophen-3-amine (**3b**).* Red solid, 111 mg (47%), mp 105–107 °C. ^{1}H NMR ($CDCl_3$) δ: 3.89 (d, J=5.7 Hz, 2H), 4.19 (br s, 1H), 5.26 (dd, J=10.2, 1.2 Hz, 1H), 5.38 (dd, J=17.4, 1.5 Hz, 1H), 5.98–6.12 (m, 1H), 6.18 (s, 1H), 7.81 (d, J=9.0 Hz, 1H), 8.13 (dd, J=9.0, 2.1 Hz, 1H), 8.48 (d, J=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 48.2, 98.1, 115.6, 117.2, 118.8, 123.5, 132.54, 134.6, 141.8, 144.7, 145.2. *m*/*z* (EI^+) 234 (M^+, 81%), 193 (34), 173 (23), 161 (43), 147 (100), 120 (21), 89 (17), 63 (31). HRMS (EI) calcd for $C_{11}H_{10}N_2O_2S$ [M^+] 234.0463, found 234.0461.

*4.2.1.3. N-Butyl-5-nitrobenzo[b]thiophen-3-amine (**3c**).* Red solid, 90 mg (36%), mp 109–110 °C. ^{1}H NMR ($CDCl_3$) δ: 1.01 (t, J=6.9 Hz, 3H), 1.45–1.57 (m, 2H), 1.69–1.79 (m, 2H), 3.23 (t, J=7.2 Hz, 2H), 6.13 (s, 1H), 7.82 (d, J=8.7 Hz, 1H), 8.14 (dd, J=8.7, 2.1 Hz, 1H), 8.48 (d, J=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 13.9, 20.4, 31.4, 45.4, 96.9, 115.6, 118.7, 123.5, 132.5, 142.5, 144.6, 145.4. *m*/*z* (EI) 250 (M^+, 59%), 207 (88), 161 (100), 147 (26), 133 (15), 89 (19). HRMS (EI) calcd for $C_{12}H_{14}N_2O_2S$ [M^+] 250.0776, found 250.0774.

*4.2.1.4. N-Benzyl-5-nitrobenzo[b]thiophen-3-amine (**3d**).* Red solid, 86 mg (30%), mp 123–126 °C. ^{1}H NMR ($CDCl_3$) δ: 4.43 (br s, N*H*, C*H*$_2$Ph, 3H), 6.16 (s, 1H), 7.29–7.45 (m, 5H), 7.82 (d, J=8.7 Hz, 1H), 8.15 (dd, J=8.7, 2.1 Hz, 1H), 8.50 (d, J=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 50.0, 98.2, 115.6, 118.8, 123.6, 127.7, 127.75, 128.8, 132.5, 138.2, 141.9, 144.7, 145.3. *m*/*z* (EI) 284 (M^+, 47%), 282 (11), 147 (18), 91 (100), 77 (8), 65 (44), 51 (20). HRMS (EI) calcd for $C_{15}H_{12}N_2O_2S$ [M^+] 284.0620, found 284.0624. Crystallographic data: CCDC 762351.

*4.2.1.5. N-iso-Propyl-5-nitrobenzo[b]thiophen-3-amine (**3e**).* Red-orange solid, 32 mg (14%), mp 148–150 °C. ^{1}H NMR ($CDCl_3$) δ: 1.34 (d, J=6.3 Hz, 6H), 3.62–3.69 (m, 1H), 3.87 (br s, 1H), 6.14 (s, 1H), 7.85 (d, J=8.7 Hz, 1H), 8.18 (dd, J=8.7, 2.1 Hz, 1H), 8.49 (d, J=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 22.8, 46.4, 97.2, 115.6, 118.8,

123.5, 132.8, 141.0, 144.7, 145.3. *m/z* (EI) 236 (M^+, 43%), 221 (100), 175 (37), 148 (29), 121 (15). HRMS (EI) calcd for $C_{11}H_{12}N_2O_2S$ [M^+] 236.0620, found 236.0618.

*4.2.1.6. N-Cyclopentyl-5-nitrobenzo[b]thiophen-3-amine (**3f**).* Red solid, 104 mg (40%), mp 142–145 °C. ^{1}H NMR ($CDCl_3$) δ: 1.72–1.87 (m, 6H), 2.05–2.12 (m, 2H), 3.81–3.88 (m, 1H), 4.02 (br s, 1H), 6.14 (s, 1H), 7.81 (d, *J*=9.0 Hz, 1H), 8.17 (dd, *J*=9.0, 2.1 Hz, 1H), 8.45 (d, *J*=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 24.3, 33.4, 56.4, 97.6, 115.6, 118.7, 123.5, 132.7, 141.7, 144.6, 145.3. *m/z* (EI) 262 (M^+, 90%), 233 (68), 220 (29), 194 (100), 173 (32), 159 (18), 148 (55), 121 (21), 69 (34). HRMS (EI) calcd for $C_{13}H_{14}N_2O_2S$ [M^+] 262.0776, found 262.0774.

*4.2.1.7. N-Cyclohexyl-5-nitrobenzo[b]thiophen-3-amine (**3g**).* Orange solid, 52 mg (19%), mp 121–123 °C. ^{1}H NMR ($CDCl_3$) δ: 1.44–1.49 (m, 5H), 1.68–1.72 (m, 1H), 1.81–1.86 (m, 2H), 2.15–2.19 (m, 2H), 3.29 (tt, *J*=9.6, 3.6 Hz, 1H), 3.90 (br s, 1H), 6.13 (s, 1H), 7.82 (d, *J*=8.7 Hz, 1H), 8.15 (dd, *J*=8.7, 2.1 Hz, 1H), 8.49 (d, *J*=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 25.0, 25.9, 33.1, 53.8, 96.9, 115.6, 118.7, 123.5, 132.8, 140.9, 144.6, 145.3. *m/z* (EI) 276 (M^+, 89%), 233 (55), 194 (58), 173 (31), 159 (18), 148 (46), 89 (14), 55 (100). HRMS (EI) calcd for $C_{14}H_{16}N_2O_2S$ [M^+] 276.0933, found 276.0928.

*4.2.1.8. N,N-Dimethyl-5-nitrobenzo[b]thiophen-3-amine (**3h**).* Orange solid, 9 mg (4%), mp 130–132 °C. IR (neat): 3124, 2953, 2832, 2787, 1598, 1568, 1501, 1473, 1422, 1265, 1245, 1196, 1172, 1145, 1098, 1086, 1038, 930, 890, 879, 848, 812, 778 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.93 (s, 6H), 6.68 (s, 1H), 7.88 (d, *J*=8.7 Hz, 1H), 8.19 (dd, *J*=8.7, 2.4 Hz, 1H), 8.73 (d, *J*=2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 44.4, 108.4, 118.3, 118.7, 123.7, 134.7, 144.9, 145.4, 149.0. *m/z* (EI) 222 (M^+, 100%), 176 (86), 160 (62), 148 (21), 134 (42), 89 (40), 63 (33). HRMS (EI) calcd for $C_{10}H_{10}N_2O_2S$ [M^+] 222.0463, found 222.0460.

*4.2.1.9. 1-(5-Nitrobenzo[b]thiophen-3-yl)pyrrolidine (**3i**).* Red solid, 78 mg (31%), mp 134–137 °C. ^{1}H NMR ($CDCl_3$) δ: 2.04–2.12 (m, 4H), 3.49–3.52 (m, 4H), 6.20 (s, 1H), 7.82 (d, *J*=9.0 Hz, 1H), 8.12 (dd, *J*=9.0, 2.1 Hz, 1H), 8.87 (d, *J*=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 25.3, 51.5, 99.9, 118.2, 119.1, 123.6, 133.7, 144.4, 145.6, 145.8. *m/z* (EI) 248 (M^+, 100%), 201 (37), 192 (24), 173 (34), 160 (43), 146 (36), 133 (20), 89 (46). HRMS (EI) calcd for $C_{12}H_{12}N_2O_2S$ [M^+] 248.0620, found 248.0615.

*4.2.1.10. 1-(5-Nitrobenzo[b]thiophen-3-yl)piperidine (**3j**).* Yellow-orange solid, 27 mg (10%), mp 143–145 °C. ^{1}H NMR ($CDCl_3$) δ: 1.61–1.69 (m, 2H), 1.81–1.88 (m, 4H), 3.04–3.11 (m, 4H), 6.74 (s, 1H), 7.87 (d, *J*=9.0 Hz, 1H), 8.17 (dd, *J*=9.0, 2.1 Hz, 1H), 8.62 (d, *J*=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 24.3, 26.2, 54.1, 109.7, 118.0, 118.7, 123.7, 135.0, 145.0, 145.2, 149.3. *m/z* (EI) 262 (M^+, 100%), 215 (24), 206 (12), 160 (41), 146 (14), 133 (36), 89 (49). HRMS (EI) calcd for $C_{13}H_{14}N_2O_2S$ [M^+] 262.0776, found 262.0776.

*4.2.1.11. 4-(5-Nitrobenzo[b]thiophen-3-yl)morpholine (**3k**).* Orange solid, 31 mg (12%), mp 183–184 °C. ^{1}H NMR ($CDCl_3$) δ: 3.14–3.17 (m, 4H), 3.96–3.99 (m, 4H), 6.83 (s, 1H), 7.90 (d, *J*=9.0 Hz, 1H), 8.20 (dd, *J*=9.0, 2.1 Hz, 1H), 8.62 (d, *J*=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 53.0, 67.0, 110.8, 117.7, 119.0, 123.9, 134.5, 145.0, 145.3, 147.8. *m/z* (EI) 264 (M^+, 96%), 206 (96), 160 (100), 146 (14), 133 (32), 89 (48). HRMS (EI) calcd for $C_{12}H_{12}N_2O_3S$ [M^+] 264.0569, found 264.0571.

*4.2.1.12. 3-Methyl-5-nitro-benzo[d]isothiazole (**11**).* A mixture of 1-(2-chloro-5-nitrophenyl)ethanone **1** (200 mg, 1.0 mmol), NH_4Cl (160 mg, 3.0 mmol), NaOAc (246 mg, 3.0 mmol), and sulfur (160 mg, 5.0 mmol) was added to 10 mL of DMF and stirred for 10 min. at 55–60 °C. The resulting dark solution was cooled to rt and DMF was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate 5:1) to afford 152 mg (78%) of the light orange product, mp 109–110 °C (Lit. Mp 114–115 °C).[26] ^{1}H NMR ($CDCl_3$) δ: 2.85 (s, 3H), 8.05 (d, *J*=8.7 Hz, 1H), 8.38 (dd, *J*=8.7, 2.1 Hz, 1H), 8.84 (d, *J*=2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 17.5, 119.6, 120.7, 121.7, 135.1, 145.6, 157.4, 164.1. *m/z* (EI) 194 (M^+, 42%), 164 (46), 148 (17), 136 (35), 121 (25), 69 (27), 63 (100).

4.3. Synthesis of 2-aminobenzo[*b*]thiophenes

*4.3.1. Ethyl 2-(1-(2-chloro-5-nitrophenyl)ethylidene)hydrazinecarboxylate (**12**).* A mixture of 1-(2-chloro-5-nitrophenyl)ethanone **1** (28.1 g, 0.14 mol), ethyl carbazate (17.5 g, 0.17 mol), and 1 mL of AcOH in 800 mL of EtOH/H_2O (1:1) was refluxed for 3 h and left overnight at rt. The precipitate was filtered, washed with EtOH/H_2O (1:1) and dried affording 37.8 g (94%) of **12** as a white solid, mp 169–170 °C. ^{1}H NMR ($CDCl_3$) δ 1.36 (t, *J*=7.0 Hz, 3H), 2.26 (s, 3H), 4.34 (q, *J*=7.0 Hz, 2H), 7.55 (d, *J*=8.7 Hz, 1H), 7.98 (br s, 1H, NH), 8.16 (dd, *J*=8.7, 2.7 Hz, 1H), 8.31 (d, *J*=2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 16.4, 62.5, 124.5, 125.8, 130.8, 139.3, 140.0, 146.6; *m/z* (EI) 285 (M^+, 20%), 250 (7), 195 (47), 178 (100), 166 (75), 151 (22), 137 (37), 102 (67); HRMS (EI) calcd for $C_{11}H_{12}ClN_3O_4$ [M^+] 285.0516, found 285.0514.

*4.3.2. 4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole (**13**).* A solution of **12** (37.5 g, 0.13 mol) in 60 mL of $SOCl_2$ was refluxed for 2 h, cooled and poured into water. The precipitate was thoroughly washed with water and dried affording 30.2 g (95%) of pure **13** as light-yellow crystals. Product **13** can be crystallized from $CHCl_3$/MeOH, mp 121 °C. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, *J*=9.0 Hz, 1H) 8.26 (dd, *J*=9.0, 2.7 Hz, 1H), 9.07 (d, *J*=2.7 Hz, 1H), 9.19 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.6, 126.8, 131.0, 131.7, 135.9, 138.8, 146.9, 156.9; *m/z* (EI): 241 (M^+, 2%), 213 (71), 167 (100), 155 (21), 132 (50), 123 (47); HRMS (EI) calcd for $C_8H_4ClN_3O_2S$ [M^+] 240.9713, found 240.9710. Crystallographic data: CCDC 762350.

4.4. General procedure for the synthesis of 2-aminobenzo[*b*]thiophenes (14a–x)

4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole **13** (0.5 g, 2.07 mmol), K_2CO_3 (0.57 g, 4.13 mmol), the corresponding amine **2a–x** (1.05–5.0 equiv), and 10 mL DMF (in that order; for molar ratios see Table 4) were charged into a 50 mL round bottom flask. The mixture was stirred for 3–22 h at 25–90 °C. DMF was removed under reduced pressure and the residue purified by column chromatography (SiO_2, $CHCl_3$/hexane (1:3), (1:2), (1:1) (2:1), or $CHCl_3$/MeOH (40:1), (100:1)) affording the corresponding 2-aminobenzo[*b*]thiophene **14a–x** (yields 6–92%, see Table 3).

*4.4.1. N-Methyl-5-nitrobenzo[b]thiophen-2-amine (**14a**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:1)). Red crystals, 0.026 g (6%), mp 163–164 °C. IR (neat): 3393, 1559, 1503, 1327, 1295, 1249, 1218, 1058, 880, 829, 809, 758, 721, 657 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.00 (d, *J*=5.1 Hz, 3H), 4.31 (br s, 1H), 6.13 (s, 1H), 7.60 (d, *J*=8.7 Hz, 1H), 7.89 (dd, *J*=8.7, 2.1 Hz, 1H), 8.24 (d, *J*=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 33.2, 95.9, 115.0, 115.3, 121.6, 138.2, 141.5, 145.9, 157.3; *m/z* (EI): 208 (M^+, 100%), 178 (10), 162 (64), 146 (14), 128 (12), 69 (13); HRMS (EI) calcd for $C_9H_8N_2O_2S$ [M^+] 208.0307, found 208.0307.

*4.4.2. N-Allyl-5-nitrobenzo[b]thiophen-2-amine (**14b**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:1)). Dark-red crystals, 0.20 g (42%), mp 67–68 °C. ^{1}H NMR ($CDCl_3$) δ 3.87 (br s, 2H), 4.50 (br s, 1H), 5.25 (dd, *J*=10.2, 1.2 Hz, 1H), 5.34 (dd, *J*=17.4, 1.5 Hz, 1H), 5.89–6.01 (m, 1H), 6.13 (s, 1H), 7.57 (d, *J*=8.7 Hz, 1H),

7.85 (dd, *J*=8.7, 2.1 Hz, 1H), 8.19 (d, *J*=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 49.2, 96.8, 115.0, 115.3, 117.5, 121.6, 133.7, 138.2, 141.4, 145.8, 156.0; *m*/*z* (EI) 234 (M^+, 100%), 207 (23), 188 (13), 161 (20); HRMS (EI) calcd for $C_{11}H_{10}N_2O_2S$ [M^+] 234.0463, found 234.0463.

*4.4.3. N-Butyl-5-nitrobenzo[b]thiophen-2-amine (**14c**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:1)). Red crystals, 0.52 g (92%), mp 74–75 °C. ^{1}H NMR ($CDCl_3$) δ 1.00 (t, *J*=7.4 Hz, 3H), 1.40–1.52 (m, 2H), 1.63–1.72 (m, 2H), 3.21–3.28 (m, 2H), 4.27 (br t, 1H), 6.12 (s, 1H), 7.59 (d, *J*=8.7 Hz, 1H), 7.87 (dd, *J*=8.7, 2.4 Hz, 1H), 8.21 (d, *J*=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8, 20.2, 31.4, 46.7, 96.0, 114.9, 115.1, 121.6, 138.0, 141.6, 145.9, 156.5; *m*/*z* (EI) 250 (M^+, 75%), 207 (100), 194 (15), 161 (65), 148 (22), 134 (16), 120 (9); HRMS (EI) calcd for $C_{12}H_{14}N_2O_2S$ [M^+] 250.0776, found 250.0776.

*4.4.4. N-Benzyl-5-nitrobenzo[b]thiophen-2-amine (**14d**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:1)). Red crystals, 0.194 g (33%), mp 99–100 °C. IR (neat): 3385, 1548, 1506, 1450, 1331, 1249, 1217, 1185, 1058, 1026, 884, 828, 809, 752, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 4.39 (d, *J*=5.1 Hz, 2H), 4.72 (br t, 1H), 6.10 (s, 1H), 7.26–7.40 (m, 5H), 7.52 (d, *J*=8.7 Hz, 1H), 7.82 (dd, *J*=8.7, 2.1 Hz, 1H), 8.13 (d, *J*=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 50.9, 96.9, 115.0, 115.3, 121.5, 127.6, 127.9, 128.8, 137.5, 138.2, 141.3, 145.8, 155.9; *m*/*z* (EI) 284 (M^+, 22%), 91 (100), 65 (20); HRMS (EI) calcd for $C_{15}H_{12}N_2O_2S$ [M^+] 284.0620, found 284.0619.

*4.4.5. N-iso-Propyl-5-nitrobenzo[b]thiophen-2-amine (**14e**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:1)). Brown crystals, 0.142 g (29%), mp 84–85 °C. ^{1}H NMR ($CDCl_3$) δ 1.32 (d, *J*=6.6 Hz, 6H), 3.62–3.69 (br m, 1H), 4.15 (br d, 1H), 6.14 (s, 1H), 7.61 (d, *J*=8.7 Hz, 1H), 7.88 (dd, *J*=8.7, 2.1 Hz, 1H), 8.23 (d, *J*=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 22.8, 48.5, 96.4, 114.8, 115.1, 121.5, 138.1, 141.6, 145.9, 155.4; *m*/*z* (EI) 236 (M^+, 97%), 221 (100), 194 (27), 175 (18), 166 (10), 148 (63), 136 (10), 121 (19), 69 (8); HRMS (EI): calcd for $C_{11}H_{12}N_2O_2S$ [M^+] 236.0620, found 236.0619.

*4.4.6. N-Cyclopentyl-5-nitrobenzo[b]thiophen-2-amine (**14f**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:1)). Dark-green crystals, 0.179 g (33%), mp 124–125 °C. ^{1}H NMR ($CDCl_3$) δ 1.64–1.82 (m, 5H), 2.02–2.12 (m, 2H), 3.78–3.88 (m, 1H), 4.31 (br d, *J*=5.1 Hz, 1H), 6.11 (s, 1H), 7.57 (d, *J*=8.7 Hz, 1H), 7.86 (dd, *J*=8.7, 2.4 Hz, 1H), 8.20 (d, *J*=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.0, 33.2, 58.1, 96.6, 114.8, 115.1, 121.5, 138.2, 141.6, 145.9, 155.8; *m*/*z* (EI) 262 (M^+, 65%), 233 (14), 194 (100), 166 (8), 148 (58), 136 (10), 121 (16), 69 (21); HRMS (EI): calcd for $C_{13}H_{14}N_2O_2S$ [M^+] 262.0776, found 262.0778.

*4.4.7. N-Cyclohexyl-5-nitrobenzo[b]thiophen-2-amine (**14g**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:1)). Red crystals, 0.217 g (38%), mp 130–131 °C. ^{1}H NMR ($CDCl_3$) δ 1.17–1.48 (m, 5H), 1.60–1.66 (m, 1H), 1.76–1.83 (m, 2H), 2.10–2.15 (m, 2H), 3.22–3.33 (m, 1H), 4.23 (br d, *J*=6.9 Hz, 1H), 6.11 (s, 1H), 7.57 (d, *J*=8.7 Hz, 1H), 7.85 (dd, *J*=8.7, 2.1 Hz, 1H), 8.19 (d, *J*=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.8, 25.6, 33.0, 55.7, 96.0, 114.6, 114.8, 121.4, 138.0, 141.6, 145.8, 155.6; *m*/*z* (EI) 276 (M^+, 52%), 233 (17), 194 (100), 166 (10), 148 (47), 136 (8), 121 (12), 83 (9), 55 (87); HRMS (EI): calcd for $C_{14}H_{16}N_2O_2S$ [M^+] 276.0933, found 276.0932.

*4.4.8. N,N-Dimethyl-5-nitrobenzo[b]thiophen-2-amine (**14h**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:2)). Red crystals, 0.35 g (75%), mp 133–134 °C. IR (neat): 3083, 2905, 2810, 1555, 1502, 1425, 1332, 1246, 1184, 1058, 908, 880, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.04 (s, 6H), 5.97 (s, 1H), 7.59 (d, *J*=8.4 Hz, 1H), 7.82 (dd, *J*=8.4, 2.4 Hz, 1H), 8.20 (d, *J*=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 42.2, 95.5, 114.4, 114.7, 121.5, 138.3, 141.8, 145.9, 159.9; *m*/*z* (EI) 222 (M^+, 100%), 207 (3), 192 (6), 176 (60), 146 (27); HRMS (EI) calcd for $C_{10}H_{10}N_2O_2S$ [M^+] 222.0463, found 222.0464.

*4.4.9. 1-(5-Nitrobenzo[b]thiophen-2-yl)pyrrolidine (**14i**) and 2-(5-nitro-2-(pyrrolidin-1-yl)phenyl)-1-(pyrrolidin-1-yl)ethanethione (**22**).* After completion of the reaction 100 mL of water was added and precipitate was filtered and washed with water. Crystallization from $CHCl_3$/EtOH afforded 0.41 g (62%) **22** as yellow needles, mp 224–225 °C. ^{1}H NMR ($CDCl_3$) δ 1.96–2.03 (m, 8H), 3.42–3.46 (m, 6H), 3.93 (t, *J*=6.0 Hz, 2H), 4.17 (s, 2H), 6.75 (d, *J*=8.7 Hz, 1H), 7.98–8.04 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.4, 25.8, 26.5, 48.5, 50.8, 51.5, 54.2, 114.2, 123.3, 124.0, 127.0, 139.2, 154.2, 197.1; calcd for $C_{16}H_{21}N_3O_2S$: C 60.16; H 6.63; N 13.15; O 10.02; S 10.04; found: C 59.94; H 6.51; N 12.83.

The solution was filtered, concentrated, and the solid residue was chromatographed (SiO_2, $CHCl_3$/Hexane (1:2)) to afford 0.036 g (7%) of **14i** as red crystals, mp 124–125 °C. ^{1}H NMR ($CDCl_3$) δ 2.07–2.12 (m, 4H), 3.37–3.41 (m, 4H), 5.89 (s, 1H), 7.60 (d, *J*=8.7 Hz, 1H), 7.81 (dd, *J*=8.7, 2.4 Hz, 1H), 8.21 (d, *J*=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.9, 50.5, 93.6, 113.9, 114.3, 121.5, 137.9, 142.0, 146.0, 156.1; *m*/*z* (EI) 248 (M^+, 100%), 202 (78); HRMS (ESI) calcd for $C_{12}H_{13}N_2O_2S$ [$M+H]^+$ 249.0691, found 249.0698.

*4.4.10. 1-(5-Nitrobenzo[b]thiophen-2-yl)piperidine (**14j**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:2)). Red crystals, 0.092 g (17%), mp 139–140 °C. ^{1}H NMR ($CDCl_3$) δ 1.58–1.76 (m, 6H), 3.28–3.31 (m, 4H), 6.18 (s, 1H), 7.62 (d, *J*=8.7 Hz, 1H), 7.87 (dd, *J*=8.7, 2.4 Hz, 1H), 8.23 (d, *J*=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.7, 25.1, 51.5, 97.3, 115.0, 115.1, 121.5, 138.5, 141.3, 145.8, 160.7; *m*/*z* (EI): 262 (M^+, 100%), 247 (13), 216 (42), 133 (16), 89 (27), 69 (24); HRMS (ESI) calcd for $C_{13}H_{15}N_2O_2S$ [$M+H]^+$ 263.0858, found 263.0854. Crystallographic data: CCDC 762349.

*4.4.11. 4-(5-Nitrobenzo[b]thiophen-2-yl)morpholine (**14k**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:2), (1:1), (2:1), $CHCl_3$). Dark-yellow crystals, 0.27 g (49%), mp 153–154 °C. ^{1}H NMR ($CDCl_3$) δ 3.28–3.31 (m, 4H), 3.87–3.90 (m, 4H), 6.28 (s, 1H), 7.67 (d, *J*=9.0 Hz, 1H), 7.94 (dd, *J*=9.0, 2.1 Hz, 1H), 8.30 (d, *J*=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 50.4, 66.1, 98.5, 115.76, 115.80, 121.8, 138.6, 140.7, 145.9, 160.2; *m*/*z* (EI) 264 (M^+, 100%), 218 (20), 206 (48), 160 (25), 133 (23); HRMS (ESI) calcd for $C_{12}H_{13}N_2O_3S$ [$M+H]^+$ 265.0636, found 265.0647.

*4.4.12. N-(1-Adamantyl)-5-nitrobenzo[b]thiophen-2-amine (**14l**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (2:1)). Dark-yellow crystals, 0.177 g (26%), mp 126–127 °C. ^{1}H NMR ($CDCl_3$) δ 1.65–1.75 (m, 6H), 1.95 (d, *J*=2.7 Hz, 6H), 2.16 (br s, 3H), 4.11 (br s, 1H), 6.34 (s, 1H), 7.58 (d, *J*=8.7 Hz, 1H), 7.88 (dd, *J*=8.7, 2.1 Hz, 1H), 8.24 (d, *J*=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.6, 36.3, 42.6, 53.9, 102.4, 115.2, 115.5, 121.4, 139.2, 140.8, 145.7, 153.2; *m*/*z* (EI) 328 (M^+, 46%), 193 (6), 166 (17), 135 (100), 107 (35); HRMS (EI) calcd for $C_{18}H_{20}N_2O_2S$ [M^+] 328.1246, found 328.1244.

*4.4.13. N-(2-Morpholinoethyl)-5-nitrobenzo[b]thiophen-2-amine (**14m**).* Purified by column chromatography (SiO_2, $CHCl_3$/MeOH (100:1)). Orange crystals, 0.388 g (61%), mp 159–160 °C. ^{1}H NMR ($CDCl_3$) δ 2.50–2.53 (m, 4H), 2.67–2.70 (m, 2H), 3.27–3.32 (m, 2H), 3.73–3.76 (m, 4H), 5.03 (br t, 1H), 6.13 (s, 1H), 7.61 (d, *J*=8.7 Hz, 1H), 7.88 (dd, *J*=8.7, 2.1 Hz, 1H), 8.23 (d, *J*=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 42.6, 53.3, 56.6, 67.0, 96.3, 115.0, 115.3, 121.6, 138.2, 141.5, 146.0, 156.3; *m*/*z* (EI): 307 (M^+, 30%), 207 (7), 161 (31), 100 (100); HRMS (EI) calcd for $C_{14}H_{17}N_3O_3S$ [M^+] 307.0991, found 307.0992.

*4.4.14. N,N-Diethyl-5-nitrobenzo[b]thiophen-2-amine (**14n**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:3), (1:2), (1:1)). Red crystals, 0.29 g (55%), mp 41–42 °C. ^{1}H NMR

($CDCl_3$) δ 1.26 (t, J=7.2 Hz, 6H), 3.40 (q, J=7.2 Hz, 4H), 5.97 (s, 1H), 7.58 (d, J=8.4 Hz, 1H), 7.81 (dd, J=8.4, 2.1 Hz, 1H), 8.18 (d, J=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 47.0, 94.2, 114.08, 114.13, 121.3, 137.7, 142.1, 145.9, 157.9; m/z (EI) 250 (M^+, 66%), 235 (100), 207 (25), 189 (23), 161 (20); HRMS (ESI) calcd for $C_{12}H_{15}N_2O_2S$ $[M+H]^+$ 251.0850, found 251.0854.

*4.4.15. N,N-Dibutyl-5-nitrobenzo[b]thiophen-2-amine (**14o**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:2)). Red crystals, 0.21 g (33%), mp 45–46 °C. ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J=7.4 Hz, 6H), 1.35–1.47 (m, 4H), 1.63–1.73 (m, 4H), 3.34 (t, J=7.5 Hz, 4H), 5.95 (s, 1H), 7.59 (d, J=8.4 Hz, 1H), 7.82 (dd, J=8.4, 2.1 Hz, 1H), 8.20 (d, J=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.2, 29.3, 53.2, 94.0, 114.0, 114.1, 121.3, 137.6, 142.2, 145.9, 158.6; m/z (EI) 306 (M^+, 46%), 263 (44), 221 (100), 207 (22), 191 (7), 175 (16), 161 (27), 57 (47); HRMS (ESI) calcd for $C_{16}H_{23}N_2O_2S$ $[M+H]^+$ 307.1473, found 307.1480.

*4.4.16. N,N-Di-iso-propyl-5-nitrobenzo[b]thiophen-2-amine (**14p**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:2)). Red crystals, 0.15 g (33%), mp 85–86 °C. ^{1}H NMR ($CDCl_3$) δ 1.35 (d, J=7.5 Hz, 12H), 3.85 (heptet, J=6.9 Hz, 2H), 6.17 (s, 1H), 7.58 (d, J=8.7 Hz, 1H), 7.82 (dd, J=8.7, 2.1 Hz, 1H), 8.21 (d, J=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.5, 51.2, 98.3, 114.4, 121.1, 137.7, 141.4, 145.8, 156.2; m/z (EI) 278 (M^+, 56%), 263 (70), 221 (100), 194 (20), 175 (26), 148(20), 121 (11); HRMS (ESI) calcd for $C_{14}H_{19}N_2O_2S$ $[M+H]^+$ 279.1162, found 279.1167.

*4.4.17. N-(Cyclopropylmethyl)-5-nitro-N-propylbenzo[b]thiophen-2-amine (**14q**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:2)). Red crystals, 0.23 g (38%), mp 48–49 °C. ^{1}H NMR ($CDCl_3$) δ 0.29 (q, J=4.8 Hz, 2H), 0.58–0.64 (m, 2H), 0.97 (t, J=7.4 Hz, 3H), 1.07–1.19 (m, 1H), 1.73 (heptet, J=7.5 Hz, 2H), 3.23 (d, J=6.6 Hz, 2H), 3.38 (t, J=7.7 Hz, 2H), 6.00 (s, 1H), 7.57 (d, J=8.7 Hz, 1H), 7.81 (dd, J=8.7, 2.1 Hz, 1H), 8.18 (d, J=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 3.9, 9.3, 11.4, 20.3, 54.7, 57.7, 94.4, 114.17, 114.20, 121.3, 137.6, 142.1, 145.9, 158.7; m/z (EI) 290 (M^+, 11%), 261 (9), 207 (10), 55 (100); HRMS (ESI) calcd for $C_{15}H_{19}N_2O_2S$ $[M+H]^+$ 291.1157, found 291.1167.

*4.4.18. N-Benzyl-N-methyl-5-nitrobenzo[b]thiophen-2-amine (**14r**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:2), (1:1), (2:1)). Red crystals, 0.25 g (41%), mp 82 °C. IR (neat): 3085, 3022, 2918, 1598, 1535, 1494, 1443, 1417, 1328, 1306, 1246, 1193, 1165, 1137, 1092, 1058, 1030, 1002, 987, 942, 917, 874, 823, 807, 793, 747, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.06 (s, 3H), 4.56 (s, 2H), 6.07 (s, 1H), 7.26–7.36 (m, 5H), 7.61 (d, J=8.7 Hz, 1H), 7.85 (dd, J=8.7, 2.1 Hz, 1H), 8.21 (d, J=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 39.7, 59.0, 95.6, 114.58, 114.66, 121.4, 127.2, 127.8, 128.8, 136.5, 138.0, 141.8, 145.9, 159.3; m/z (EI) 298 (M^+, 20%), 91 (100); HRMS (ESI) calcd for $C_{16}H_{15}N_2O_2S$ $[M+H]^+$ 299.0843, found 299.0854.

*4.4.19. N-tert-Butyl-5-nitrobenzo[b]thiophen-2-amine (**14s**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:1)). Yellow crystals, 0.20 g (39%), mp 114–115 °C. IR (neat): 3347, 3109, 2970, 1508, 1469, 1335, 1204, 1060, 903, 827, 796 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 4.18 (br s, 1H), 6.31 (s, 1H), 7.61 (d, J=8.7 Hz, 1H), 7.90 (dd, J=8.7, 2.1 Hz, 1H), 8.26 (d, J=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.3, 53.6, 101.2, 115.3, 115.6, 121.4, 138.9, 141.1, 145.8, 153.8; m/z (EI) 250 (M^+, 37%), 194 (100), 148 (46), 121 (12), 57 (69); HRMS (EI) calcd for $C_{12}H_{14}N_2O_2S$ [M^+] 250.0776, found 250.0775.

*4.4.20. Ethyl 2-(5-nitrobenzo[b]thiophen-2-ylamino)acetate (**14t**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (2:1)). Yellow crystals, 0.052 g (9%), mp 163–164 °C. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J=7.2 Hz, 3H), 4.01 (d, J=5.1 Hz, 2H), 4.29 (q, J=7.2 Hz, 2H), 4.95 (br t, 1H), 6.13 (s, 1H), 7.62 (d, J=8.7 Hz, 1H), 7.91 (dd, J=8.7, 2.4 Hz, 1H), 8.25 (d, J=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 47.8, 61.9, 97.4, 115.5, 115.8, 121.7, 138.4, 141.1, 145.9, 154.7, 169.7; m/z (EI) 280 (M^+, 30%), 207 (100), 161 (34), 134 (10); HRMS (EI) calcd for $C_{12}H_{12}N_2O_4S$ [M^+] 280.0519, found 280.0519.

*4.4.21. N-(2-(1H-Indol-3-yl)ethyl)-5-nitrobenzo[b]thiophen-2-amine (**14u**).* Purified by column chromatography (SiO_2, $CHCl_3$/MeOH (100:1)). Yellow crystals, 0.20 g (23%), mp 160–161 °C. ^{1}H NMR ($CDCl_3$) δ 3.15 (t, J=6.5 Hz, 2H), 3.57 (q, J=6.5 Hz, 2H), 4.35 (br t, J=5.3 Hz, 1H), 6.13 (s, 1H), 7.08 (d, J=2.4 Hz, 1H), 7.13–7.18 (m, 1H), 7.21–7.27 (m, 1H), 7.40 (d, J=7.8 Hz, 1H), 7.57 (d, J=8.7, Hz, 1H), 7.62 (d, J=7.8 Hz, 1H), 7.86 (dd, J=8.7, 2.4 Hz, 1H), 8.09 (br s, 1H), 8.20 (d, J=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.0, 46.9, 96.5, 111.4, 112.5, 115.0, 115.2, 121.6, 122.3, 122.5, 127.2, 136.5, 138.2, 141.5, 145.9, 156.3; m/z (EI) 337 (M^+, 8%), 207 (7), 143 (8), 130 (100); HRMS (EI) calcd for $C_{18}H_{15}N_3O_2S$ [M^+] 337.0885, found 337.0882.

*4.4.22. 2,6-Dimethyl-1-(5-nitrobenzo[b]thiophen-2-yl)piperidine (**14v**).* Purified by column chromatography (SiO_2, $CHCl_3$/Hexane (1:2), (1:1)). Orange crystals, 0.38 g (63%), mp 98–99 °C. ^{1}H NMR ($CDCl_3$) δ 1.19 (d, J=6.9 Hz, 6H), 1.58–1.62 (m, 3H), 1.82–1.85 (m, 3H), 3.50–3.54 (m, 2H), 6.35 (s, 1H), 7.66 (d, J=8.7 Hz, 1H), 7.91 (dd, J=8.7, 2.4 Hz, 1H), 8.30 (d, J=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.0, 19.5, 31.8, 54.5, 102.3, 115.5, 115.7, 121.9, 139.8, 140.4, 145.7, 159.4; m/z (EI) 290 (M^+, 33%), 275 (100), 81 (15), 55 (65); HRMS (ESI) calcd for $C_{15}H_{19}N_2O_2S$ $[M+H]^+$ 291.1164, found 291.1167.

*4.4.23. 2-(1-(5-Nitrobenzo[b]thiophen-2-yl)piperidin-2-yl)ethanol (**14w**).* Purified by column chromatography (SiO_2, $CHCl_3$/MeOH (100:1)). Red-orange crystals, 0.127 g (20%), mp 114–115 °C. ^{1}H NMR ($CDCl_3$) δ 1.53–1.75 (m, 5H), 1.80–1.92 (m, 2H), 2.01–2.08 (m, 1H), 3.12–3.27 (m, 1H), 3.47–3.51 (m, 1H), 3.71–3.76 (m, 2H), 3.97–4.03 (m, 1H), 6.18 (s, 1H), 7.59 (d, J=8.4 Hz, 1H), 7.84 (dd, J=8.4, 2.4 Hz, 1H), 8.20 (d, J=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.7, 24.7, 27.4, 31.1, 45.7 55.5, 60.2, 96.5, 114.76, 114.79, 116.7, 121.5, 124.9, 138.9, 141.6, 145.8, 159.9; m/z (EI) 306 (M^+, 22%), 289 (14), 261 (100), 215 (23); HRMS (ESI) calcd for $C_{15}H_{19}N_2O_3S$ $[M+H]^+$ 307.1108, found 307.1116.

*4.4.24. 1-Methyl-4-(5-nitrobenzo[b]thiophen-2-yl)piperazine (**14x**).* Purified by column chromatography (SiO_2, $CHCl_3$/MeOH (40:1)). Yellow crystals, 0.43 g (74%), mp 139–140 °C. ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 2.58–2.62 (m, 4H), 3.33–3.36 (m, 4H), 6.23 (s, 1H), 7.65 (d, J=8.7 Hz, 1H), 7.91 (dd, J=8.7, 2.4 Hz, 1H), 8.27 (d, J=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 46.1, 50.3, 54.2, 98.4, 115.56, 115.59, 121.7, 138.7, 141.0, 145.9, 160.1; m/z (EI): 277 (M^+, 100%), 220 (14), 206, (13), 192 (34), 160 (14), 146 (9), 133 (16); HRMS (ESI) calcd for $C_{13}H_{16}N_3O_2S$ $[M+H]^+$ 278.0959, found 278.0963.

*4.4.25. Ethyl 2-(1-(2-chlorophenyl)ethylidene)hydrazinecarboxylate (**24**).* A mixture of 1-(2-chlorophenyl)ethanone **23** (3 g, 19.4 mmol), ethyl carbazate (2.42 g, 23.3 mmol), and one drop of AcOH in 40 mL of EtOH/H_2O (1:1) was refluxed for 3 h and left overnight at rt. The precipitate was filtered, washed with EtOH/H_2O (1:1) and dried affording 2.19 g (47%) of **24** as white crystals, mp 130–131 °C. ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J=7.1 Hz, 3H), 2.22 (s, 3H), 4.33 (q, J=7.1 Hz, 2H), 7.26–7.30 (m, 2H), 7.35–7.38 (m, 1H), 7.41–7.44 (m, 1H), 7.93 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.6, 16.8, 62.2, 126.9, 129.7, 129.9, 130.5, 132.3, 138.8, 149.5; m/z (EI) 240 (M^+, 13%), 205 (33), 161 (30), 152 (26), 133 (100), 126 (25), 111 (7); HRMS (EI) calcd for $C_{11}H_{13}ClN_2O_2$ [M^+] 240.0666, found 240.0664.

*4.4.26. 4-(2-Chlorophenyl)-1,2,3-thiadiazole (**25**).* A solution of **24** (2.0 g, 8.32 mmol) in 6 mL of $SOCl_2$ was refluxed for 2 h, cooled and poured into water. The precipitate was thoroughly washed with water and dried affording 1.3 g (79%) of pure **25** as light-brown

crystals, mp 30–31 °C. ^{1}H NMR ($CDCl_3$) δ 7.37–7.47 (m, 2H), 7.53–7.57 (m, 1H), 8.12–8.16 (m, 1H), 9.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 127.4, 129.6, 130.4, 130.6, 131.9, 132.3, 134.6, 159.1; *m*/*z* (EI) 196 (M^+, 5%), 168 (100), 133 (49), 89 (48); HRMS (EI) calcd for $C_8H_5ClN_2S$ [M^+] 195.9862, found 195.9862.

*4.4.27. N-Butyl-2-(2-chlorophenyl)ethanethioamide (**26**).* A mixture of **25** (0.086 g, 0.43 mmol), K_2CO_3 (0.18 g, 1.3 mmol), and *n*-butylamine (0.16 g, 2.19 mmol) in 10 mL DMF was heated and stirred at 130 °C for 24 h. After cooling to rt, the solvent was evaporated under vacuum. The residue was dissolved in $CHCl_3$ and thoroughly washed with water. Evaporation of the $CHCl_3$ afforded 0.088 g (97%) of pure **26** as a brown oil. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J*=7.5 Hz, 3H), 1.25–1.35 (m, 2H), 1.49–1.58 (m, 2H), 3.61 (t, *J*=7.5 Hz, 2H), 4.22 (s, 2H), 7.27–7.33 (m, 2H), 7.38–7.46 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.0, 29.8, 45.9, 50.2, 127.5, 129.3, 129.8, 131.9, 133.3, 134.3, 200.2; *m*/*z* (EI) 206 (M^+, 100%), 164 (7), 150 (27), 134 (9), 125 (15), 89 (15), 57 (16).

*4.4.28. 2-Methoxy-5-nitrobenzo[b]thiophene (**29**).* Na (0.29 g, 12.42 mmol) was dissolved in 50 mL of dry MeOH. Compound **13** (1.0 g, 4.14 mmol) was added to the resulting solution and the mixture was stirred and refluxed for 24 h under an atmosphere of argon. After cooling, several drops of AcOH were added to neutralize the mixture. The solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2, EtOAc/Hexane (1:8)) affording 0.2 g (23%) of **29**, as yellow crystals, mp 118 °C. IR (neat): 3087, 3021, 2943, 1601, 1550, 1507, 1443, 1336, 1296, 1250, 1208, 1193, 1163, 1138, 1056, 977, 939, 900, 828, 812, 792, 723, 653 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 4.04 (s, 3H), 6.46 (s, 1H), 7.70 (d, *J*=8.7 Hz, 1H), 8.04 (dd, *J*=8.7, 2.4 Hz, 1H), 8.40 (d, *J*=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 60.0, 98.3, 116.9, 117.0, 122.3, 138.2, 138.7, 145.7, 168.1; *m*/*z* (EI) 209 (M^+, 100%), 194 (15), 166 (55), 136 (22), 120 (85); HRMS (EI); calcd for $C_9H_7NO_3S$ [M^+] 209.0147, found 209.0148.

*4.4.29. 4-Nitro-2-(1,2,3-thiadiazol-4-yl)benzenethiol (**31**).* A mixture of **13** (0.3 g, 1.24 mmol), K_2CO_3, (0.52 g, 3.73 mmol), and potassium thioacetate (0.42 g, 3.73 mmol) in DMF (10 mL) was stirred and heated at 70 °C for 12 h. The solvent was evaporated under reduced pressure. The residue was dissolved in 200 mL of water and stirred with charcoal for 10 min at rt. The charcoal was filtered and the resulting solution was acidified with aqueous HCl (3 M) to form a yellow precipitate. The precipitate was filtered and thoroughly washed with water to yield 1.9 g (80%) of **31** as yellow powder, mp 116–117 °C. ^{1}H NMR ($CDCl_3$) δ 4.77 (s, 1H), 7.60 (d, *J*=8.7 Hz, 1H), 8.15 (dd, *J*=8.7, 2.7 Hz, 1H), 8.58 (d, *J*=2.7 Hz, 1H), 8.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 123.9, 125.8, 116.9, 129.4, 131.1, 135.1, 142.2, 159.4; *m*/*z* (EI) 237 ([M−2]$^+$, 52%), 209 (74), 165 (84), 153 (24), 132 (17), 121 (100); HRMS (EI) calcd for $C_8H_5N_3O_2S_2$ [M^+] 238.9823, found 238.9825.

*4.4.30. (E)-2-(2-Chloro-5-nitrobenzylidene)-4-(2-chloro-5-nitrophenyl)-1,3-dithiole (**32**).* A mixture of compound **13** (0.5 g, 2.07 mmol) and K_2CO_3, (0.86 g, 6.21 mmol) in MeCN (20 mL) was stirred and refluxed for 6 h. After cooling to rt, the mixture was poured into water (200 mL) and refluxed for an additional 1 h. The precipitate was filtered and thoroughly washed with water to yield 0.42 g (95%) of **32** as orange powder, mp 220–223 °C. ^{1}H NMR (DMSO-d_6) δ 6.92 (s, 1H), 7.36 (s, 1H), 7.79 (d, *J*=8.7 Hz, 1H), 7.89 (d, *J*=9.0 Hz, 1H), 8.02 (dd, *J*=8.7, 2.7 Hz, 1H), 8.24 (d, *J*=2.7 Hz, 1H), 8.27 (dd, *J*=9.0, 2.7 Hz, 1H), 8.34 (d, *J*=2.7 Hz, 1H). *m*/*z* (EI) 426 (M^+, 100%), 390 (18), 298 (8), 264 (13), 199 (58), 164 (19), 155 (43), 132 (28), 123 (19); HRMS (EI) calcd for $C_{16}H_8Cl_2N_2O_4S_2$ [M^+] 425.9303, found 425.9305.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.01.069.

References and notes

1. Grese, T. A.; Pennington, L. D.; Sluka, J. P.; Adrian, M. D.; Cole, H. W.; Fuson, T. R.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Shetler, P. K.; Short, L. L.; Venugopalan, M.; Yang, N. N.; Sato, M.; Glasebrook, A. L.; Bryant, H. U. *J. Med. Chem.* **1998**, *41*, 1272–1283.
2. Grese, T. A.; Cho, S.; Finley, D. R.; Godfrey, A. G.; Jones, C. D.; Lugar, C. W.; Martin, M. J.; Matsumoto, K.; Pennington, L. D.; Winter, M. A.; Adrian, M. D.; Cole, H. W.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Short, L. L.; Glasebrook, A. L.; Bryant, H. U. *J. Med. Chem.* **1997**, *40*, 146–167.
3. Lee, K. C.; Moon, B. C.; Lee, J. H.; Chung, K.-H.; Katzenellenbogen, J. A.; Chi, D. Y. *Bioorg. Med. Chem.* **2003**, *11*, 3649–3658.
4. Takeuchi, K.; Kohn, T. J.; Sall, D. J.; Denney, M. L.; McCowan, J. R.; Smith, G. F.; Gifford-Moore, D. S. *Bioorg. Med. Chem.* **1999**, *9*, 759–764.
5. Pinto, E.; Queiroz, M.-J. R. P.; Vale-Silva, L. A.; Oliveira, J. F.; Begouin, A.; Begouin, J.-M.; Kirsch, G. *Bioorg. Med. Chem.* **2008**, *16*, 8172–8177.
6. Queiroz, M.-J. R. P.; Begouin, A.; Ferreira, I. C. F. R.; Kirsch, G.; Calhelha, R. C.; Barbosa, S.; Estevinho, L. M. *Eur. J. Org. Chem.* **2004**, 3679–3685.
7. Stacy, G. W.; Villaescusa, F. W.; Wollner, T. E. *J. Org. Chem.* **1965**, *30*, 4074–4078.
8. Grandclaudon, P.; Lablache-Combier, A. *J. Org. Chem.* **1978**, *43*, 4379–4381.
9. Brower, K. R.; Amstutz, E. D. *J. Org. Chem.* **1954**, *19*, 411–414.
10. Benincori, T.; Sannicolo, F. *J. Org. Chem.* **1988**, *53*, 1309–1312.
11. David, E.; Perrin, J.; Pellet-Rostaing, S.; Fournier dit Chabert, J.; Lemaire, M. *J. Org. Chem.* **2005**, *70*, 3569–3573.
12. Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965–3968.
13. Ferreira, I. C. F. R.; Queiroza, M.-J. R. P.; Kirsch, G. *Tetrahedron* **2003**, *59*, 3737–3743.
14. Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861–2873.
15. Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793–796.
16. Boswell, D. E.; Brennan, J. A.; Landis, P. S.; Rodewald, P. G. *J. Heterocycl. Chem.* **1968**, *5*, 69–75.
17. Toselli, M.; Spagnolo, P.; Zanirato, P. *Gazz. Chim. Ital.* **1989**, *119*, 411–413.
18. Carrington, D. E. L.; Clarke, K.; Scrowston, R. M. *J. Chem. Soc. C* **1971**, 3903–3906.
19. Hallas, G.; Towns, A. D. *Dyes Pigm.* **1997**, *35*, 219–237.
20. Bridges, A. J.; Zhou, H. *J. Heterocycl. Chem.* **1997**, *34*, 1163–1172.
21. Solovyev, A. Y.; Androsov, D. A.; Neckers, D. C. *J. Org. Chem.* **2007**, *72*, 3122–3124.
22. Androsov, D. A.; Neckers, D. C. *J. Org. Chem.* **2007**, *72*, 5368–5373.
23. Androsov, D. A. *J. Org. Chem.* **2008**, *73*, 8612–8614.
24. Mundy, B. P.; Ellerd, M. G.; Favaloro, F. G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed.; Wiley-Interscience: Hoboken, 2005.
25. Zbruev, O. I.; Stiasni, N.; Kappe, C. O. *J. Comb. Chem.* **2003**, *5*, 145–148.
26. Kameswaran, V. US Patent 6,355,796 B1, 2002.
27. Schwenk, E.; Bloch, E. *J. Am. Chem. Soc.* **1942**, *64*, 3051–3052.
28. Klingele, M. H.; Brooker, S. *Eur. J. Org. Chem.* **2004**, 3422–3434.
29. Poupaert, J. H.; Duarte, S.; Colacino, E.; Depreux, P.; McCurdy, C. M.; Lambert, D. L. *Phosphorus Sulfur Silicon Relat. Elem.* **2004**, *179*, 1959–1973.
30. Aghapoor, K.; Darabi, H.-R.; Tabar-Heydar, K. *Phosphorus Sulfur Silicon Relat. Elem.* **2002**, *177*, 1183–1187.
31. Aghapoor, K.; Darabi, H.-R.; Tabar-Heydar, K. *Phosphorus Sulfur Silicon Relat. Elem.* **2002**, *177*, 1189–1192.
32. Schroth, W.; Andersch, J. *Synthesis* **1989**, 202–204.
33. Butler, R. N.; O'Donoghue, D. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1223–1227.
34. Hurd, C. D.; Mori, R. I. *J. Am. Chem. Soc.* **1955**, *77*, 5359–5364.
35. Raap, R.; Micetich, R. G. *Can. J. Chem.* **1968**, *46*, 1057–1063.
36. Mayer, R.; Hunger, B.; Prousa, R.; Muller, A. K. *J. Prakt. Chem.* **1967**, *35*, 294–301.
37. Shafiee, A.; Lalezari, I. *J. Heterocycl. Chem.* **1973**, *10*, 11–14.
38. Caddy, B.; Martin-Smith, M.; Norris, R. K.; Reid, S. T.; Sternhell, S. *Aust. J. Chem.* **1968**, *21*, 1853–1866.
39. Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409–2411.
40. Cook, A. G. *Enamines: Synthesis, Structures and Reactions*; Marcel Dekker: New York & London, NY, 1969.