DOI: 10.1002/ejoc.200900845

Triethylamine-Catalyzed Domino Reactions of 1,3-Thiazolidinedione: A Facile Access to Functionalized Dihydrothiophenes

Jing Sun,[a] Er-Yan Xia,[a] Li-Li Zhang,[a] and Chao-Guo Yan*[a]

Keywords: Domino reactions / Multicomponent reactions / Cyclization / Heterocycles / Amines

In the presence of triethylamine as base catalyst, aromatic amines have successfully been used as substrates in the domino reactions of 1,3-thiazolidinedione, malononitrile, and aromatic aldehydes. Through a domino ring-opening/recyclization process of 1,3-thiazolidinedione, a series of polysubstituted dihydrothiophenes in the *trans* configuration have been synthesized in high yields. Dihydrothiophene derivatives can be converted efficiently into the corresponding thiophenes by oxidation with DDQ under mild conditions.

Multicomponent reactions (MCRs) involving domino processes, with at least three different substrates reacting in a well-dened manner to form a single compound, have emerged as a powerful tool in organic synthesis.[1,2] In recent years MCRs have attracted considerable attention due to their rapid elaboration of complex structures in a highly efficient and modular manner, and the formation of several bonds in a single step is highly compatible with the goals of "green chemistry" and atom economy.[3,4] The application of this strategy in the synthesis of heterocycles has recently become an attractive field because of the important role of these targets in natural products, pharmaceuticals, and functional materials.[5,6] The synthesis of heterocycles by multicomponent reactions often involves classic carbonyl condensation chemistry.[7,8] Among carbonyl compounds, 1,3-dicarbonyl derivatives are important synthetic intermediates, incorporating multiple functionalities that can act as either nucleophilic or electrophilic species in a variety of synthetic transformations.[9] The high synthetic potential of these easily accessible reagents has found numerous applications, especially in the synthesis of complex heterocyclic structures. 1,3-Thiazolidinedione is a heterocyclic compound with an active methylene group that has been used in many condensation reactions.[10–13] Recently we reported a novel domino reaction involving 1,3-thiazolidinedione, malononitrile, aromatic aldehydes, and amines.[14] The reaction is unique because the ring-opening/recyclization or spiro-cyclization process unexpectedly occurs at the 1,3-thiazolidinedione ring with different kinds of amines, and dihydrothiophene or spirocyclohexane[1,3]-thiazole derivatives, which are normally difficult to prepare,[15–17] are obtained in a very convenient manner. To obtain more information about the mechanism of this multicomponent reaction and to examine the substrate scope and its limitations, we have investigated the reactivity of versatile amines in the reaction and found very interesting results. Herein we wish to report the reactivity of aromatic amines in the above-mentioned multicomponent reactions.

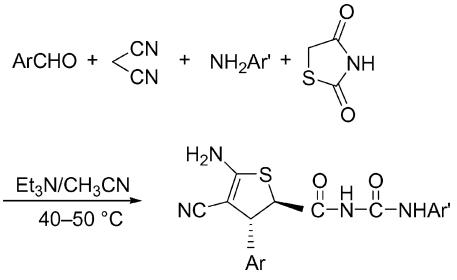
[a] College of Chemistry & Chemical Engineering, Yangzhou University,
Yangzhou 225002, P. R. China
E-mail Address: cgyan@yzu.edu.cn

Results and Discussion

In the four-component reactions of 1,3-thiazolidinedione, malononitrile, aromatic aldehydes, and amines we found that the structure of the amine played an important role. Secondary amines such as pyrrolidine, piperidine, morpholine, and dimethylamine and primary amines such as benzylamine yield dihydrothiophene derivatives by a domino ring-opening/recyclization reaction of 1,3-thiazolidinedione.[11] It was very interesting to investigate the reactivity of aromatic amines in this multicomponent reaction. At first *p*-toluidine was chosen as a substrate for the reaction. When equimolar amounts of benzaldehyde, malononitrile, 1,3-thiazolidinedione, and *p*-toluidine in acetonitrile were stirred at room temperature for 2 days, a complex mixture of products was formed from which Knoevenagel condensation products of benzaldehyde with malononitrile and benzaldehyde with 1,3-thiazolidinedione among others were detected. This result means that the basicity of the aromatic amine is probably too weak to promote the ring cleavage of 1,3-thiazolidinedione. Other base catalysts, such as sodium and potassium carbonate and pyridine, were added to the reaction and some expected products were formed along with some byproducts. The best result was obtained by adding triethylamine as a base catalyst, which gave the dihydrothiophene derivative **1a** in about 20% yield after 4 days at room temperature. At an elevated temperature (40–

50 °C) the yield of **1a** (Table 1, entry 1) was increased to 47% and at reflux a complex mixture was formed. Thus, with triethylamine as the base catalyst and *p*-toluidine as a nucleophile, the domino ring-opening/recyclization reaction of 1,3-thiazolidinedione with benzaldehyde and malononitrile took place smoothly at 50 °C. Encouraged by these results, we investigated the reactions of various aromatic aldehydes with different substituents under these optimal reaction conditions. The results are collected in Table 1 and show that all of the reactions proceeded smoothly to afford the corresponding dihydrothiophenes **1b**–**1i** in moderate-to-good yields (38–72%). Aromatic aldehydes carrying either electron-donating or -withdrawing substituents showed similar reactivity and reacted efficiently to yield the desired dihydrothiophene as the main product. Thus, our present protocol provides an expedient method for the synthesis of dihydrothiophene compounds.[15–17]

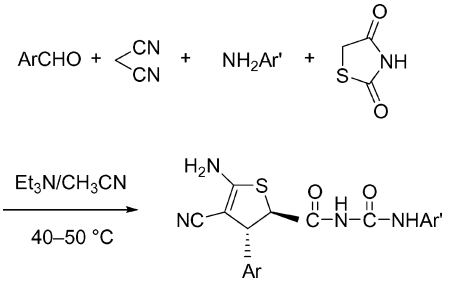
Table 1. Synthesis of dihydrothiophenes by one-pot four-component reactions.



Entry		Ar′	Ar	Yield [%]
1	**1a**	*p*-$CH_3C_6H_4$	Ph	47
2	**1b**	*p*-$CH_3C_6H_4$	*p*-$H_3CC_6H_4$	65
3	**1c**	*p*-$CH_3C_6H_4$	*p*-$(CH_3)_2CHC_6H_4$	47
4	**1d**	*p*-$CH_3C_6H_4$	*p*-HOC_6H_4	66
5	**1e**	*p*-$CH_3C_6H_4$	*p*-$H_3COC_6H_4$	72
6	**1f**	*p*-$CH_3C_6H_4$	*p*-FC_6H_4	51
7	**1g**	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	54
8	**1h**	*p*-$CH_3C_6H_4$	*p*-BrC_6H_4	66
9	**1i**	*p*-$CH_3C_6H_4$	*m*-$O_2NC_6H_4$	38

To further explore the scope of this four-component reaction, a variety of substituted arylamines were tested under the optimal reaction conditions. The results are summarized in Table 2. In general, aniline and arylamines containing *p*-chloro, *m*-chloro, and 2,4-dichloro groups, as well as α-naphthylamine, gave dihydrothiophene derivatives **2a**–**2m** in acceptable yields. But *p*-nitroaniline gave a very low yield of the product **2n** (28%), which might be due to the very low nucleophilicity of *p*-nitroaniline caused by the strongly electron-withdrawing nitro group. The structures of the prepared dihydrothiophenes **1a**–**1i** and **2a**–**2m** were determined by elemental analysis and ^1H and ^{13}C NMR, MS, and IR spectroscopy, which were further confirmed by single-crystal X-ray diffraction studies performed on the representative compounds **1e**, **2c**, **2f**, **2i**, **2j**, and **2l**. In the ^1H NMR spectrum of dihydrothiophene **1a** the 5-amino group shows a singlet at 7.19 ppm and the two NH units display two broad peaks at 10.66 and 10.15 ppm. The two protons at the 2- and 3-positions of the dihydrothiophene ring display two singlets at 4.60 and 4.20 ppm. The ^1H NMR spectra of the other dihydrothiophenes also show two singlets or slightly broad peaks at around 4.60 and 4.20 ppm for the two protons at the 2- and 3-positions of the thiophene ring, which strongly suggests that only one stereoisomer of the product exists. The molecular structures of the six dihydrothiophenes determined by X-ray diffraction also clearly show that the two substituents at the 2- and 3-positions are in a *trans* configuration and that the 4-cyano and 5-amino groups are connected to a C=C double bond. The molecular structure of **2c** is shown in Figure 1. Thus, we can conclude that only *trans* dihydrothiophenes were produced in the reaction and that this four-component reaction is a diastereoselective reaction. Note that under these new reaction conditions aromatic amines usually gave higher yields of dihydrothiophenes than the aliphatic amines studied in our previous work.[14]

Table 2. Synthesis of dihydrothiophenes by one-pot four-component reactions.



Entry		Ar′	Ar	Yield [%]
1	**2a**	*p*-ClC_6H_4	Ph	54
2	**2b**	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	62
3	**2c**	*p*-ClC_6H_4	*p*-FC_6H_4	57
4	**2d**	*p*-ClC_6H_4	*p*-ClC_6H_4	67
5	**2e**	*p*-ClC_6H_4	*m*-$O_2NC_6H_4$	44
6	**2f**	Ph	Ph	50
7	**2g**	Ph	*p*-$CH_3OC_6H_4$	80
8	**2h**	Ph	*p*-ClC_6H_4	75
9	**2i**	Ph	*p*-BrC_6H_4	79
10	**2j**	α-Naph	*p*-$CH_3OC_6H_4$	60
11	**2k**	*o*-ClC_6H_4	*p*-$CH_3OC_6H_4$	78
12	**2l**	*m*-ClC_6H_4	*p*-$CH_3OC_6H_4$	56
13	**2m**	2,4-$Cl_2C_6H_4$	*p*-$CH_3OC_6H_4$	57
14	**2n**	*p*-$O_2NC_6H_4$	*p*-$CH_3OC_6H_4$	28

This domino reaction proceeds in a very straightforward manner. To explain the formation of dihydrothiophenes by this one-pot domino multicomponent reaction, we have proposed a plausible reaction mechanism, which is illustrated in Scheme 1. The first step is the deprotonation of 1,3-thiazolidinedione by triethylamine to form a carbanion intermediate and the formation of arylidenemalononitrile **A** derived from the Knoevenagel condensation of an aromatic aldehyde with malononitrile catalyzed by triethylamine. The second step is the Michael addition of the carbanion of 1,3-thiazolidinedione to arylidenemalononitrile **A** to yield the adduct **B**. The arylamine then attacks the carbonyl group of thiazolidinedione in a ring-opening reaction to give a

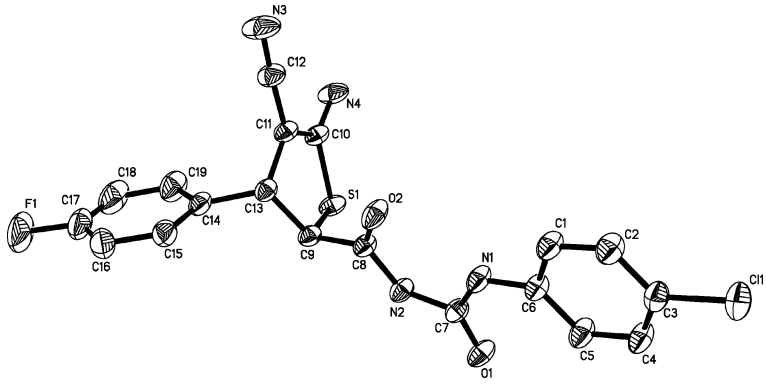
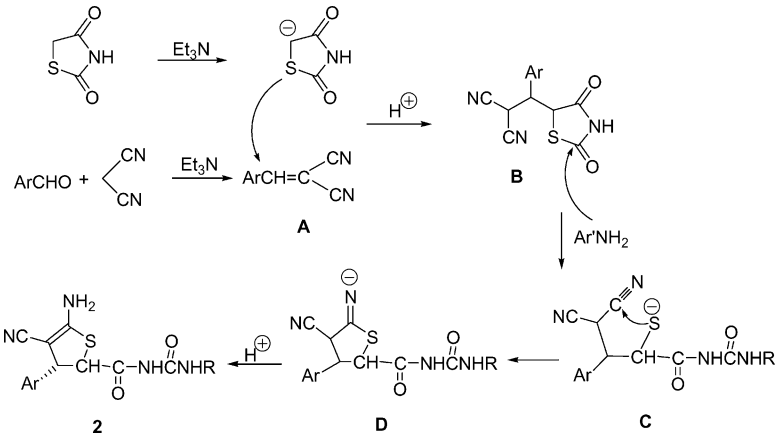


Figure 1. The molecular structure of **2c**.

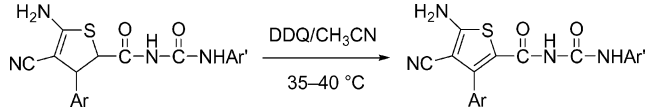


Scheme 1. Proposed mechanism for the formation of polyfunctional dihydrothiophenes.

sulfide anion **C**, which intramolecularly nucleophilically attacks one of the cyano groups to form sulfur-containing five-membered ring intermediate **D**. Finally, the 2,3-dihydrothiophene is produced through an imine–enamine tautomerization process. In the cyclization step the sterically large 4-aryl and 5-ureidoformamide groups would prefer stereochemically opposite positions to reduce the steric hindrance in the sulfide anion **C** and in the transition state of the cyclization step. Thus, only the *trans* isomeric 2,3-dihydrothiophene was produced after cyclization. In this proposed reaction mechanism triethylamine acts as a base to catalyze the Knoevenagel condensation and Michael addition reaction, whereas the arylamine behaves as a nucleophilic reagent to complete the intermolecular substitution reaction.

We were interested in exploring the aromatization of the above prepared dihydrothiophenes to thiophenes. By using DDQ as the oxidant, the suspensions of some representative dihydrothiophenes were stirred in acetonitrile at 35–40 °C for several hours, which gave the corresponding thiophenes **3a**–**3e** efficiently in very high yields (Table 3). Thus, this protocol provides an expedient method for the synthesis of polysubstituted thiophene derivatives. The ^{1}H NMR spectra of thiophenes **3a**–**3e** clearly show the disappearance of the two protons at the 2- and 3-positions of the corresponding dihydrothiophene. Note that the amino group in **3c** shows a singlet at δ = 8.13 ppm, which is greatly shifted to a lower magnetic field relative to the signal of the amino group in the corresponding dihydrothiophene **1h** (δ = 7.25 ppm). The single-crystal structures of **3a** (Figure 2) and **3e** also reveal the formation of the thiophene ring. In the molecular structure of **3e** the two C=C double bond lengths of C12–C13 and C11–C15 are 1.393(2) and 1.375(2) Å, and the two C–S bond lengths are 1.7510(19) and 1.7265(19) Å.

Table 3. Synthesis of thiophenes by dehydrogenation.



Entry		Ar′	Ar	Yield [%]
1	**3a**	Ph	*p*-ClC_6H_4	93
2	**3b**	*p*-ClC_6H_4	*p*-ClC_6H_4	95
3	**3c**	*p*-$CH_3C_6H_4$	*p*-BrC_6H_4	94
4	**3d**	Ph	*p*-BrC_6H_4	95
5	**3e**	*p*-ClC_6H_4	*m*-$O_2NC_6H_4$	90

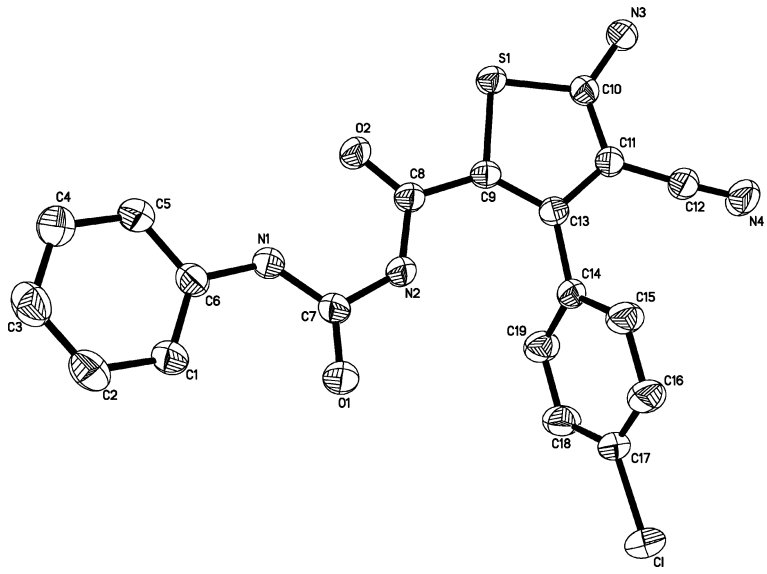


Figure 2. The molecular structure of **3a**.

Conclusions

We have extended the scope of the previously discovered tandem reactions of 1,3-thiazolidinedione, malononitrile, aromatic aldehydes, and amines. Polysubstituted dihydrothiophenes with a *trans* configuration and the corresponding thiophene derivatives have been efficiently prepared in moderate yields by a domino ring-opening/recyclization reaction of 1,3-thiazolidinedione. The advantages of this approach are as follows: The reaction procedure is convenient, involving a simple experimental procedure and product isolation, thus dispensing with extensive recrystallization or chromatographic purification steps. It is a four-component reaction that allows the construction of relatively complex sulfur-containing heterocyclic systems by using simple starting materials. Thus, our present protocol provides an expedient method for the diastereomeric synthesis of dihydrothiophene compounds.

Experimental Section

General Procedure for the Preparation of Dihydrothiophenes by a One-Pot Four-Component Reaction of 1,3-Thiazolidinedione, Aromatic Aldehydes, Malononitrile, and *p*-Toluidine: A mixture of aromatic aldehyde (4.0 mmol), malononitrile (4.0 mmol, 0.264 g), and triethylamine (1.0 mmol, 0.101 g) in acetonitrile (5.0 mL) was stirred at room temperature for 2 min. Then *p*-toluidine (4.0 mmol, 0.428 g) and 1,3-thiazolidinedione (4.0 mmol) were added and the reaction was stirred at 40 °C for an additional 48 h. The resulting precipitate was collected by filtration and washed with acetonitrile. The crude product was recrystallized with a mixture of acetonitrile and *N*,*N*-dimethylformamide to give the pure products **1a**–**1i**.

1a: White solid, 47%, m.p. >250 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.66 (br. s, 1 H, NH), 10.15 (br. s, 1 H, NH), 7.42–7.37 (m, 4 H, ArH), 7.34–7.29 (m, 3 H, ArH), 7.19 (s, 2 H, NH$_2$), 7.13 (d, J = 7.8 Hz, 2 H, ArH), 4.60 (s, 1 H, CH), 4.20 (s, 1 H, CH), 2.26 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.3, 161.7, 150.5, 141.5, 134.9, 132.8, 129.3, 128.7, 127.5, 127.1, 119.8, 118.1, 70.4, 55.3, 51.6, 20.3, 18.6 ppm. IR (KBr): $\tilde{\nu}$ = 3439, 3304, 3200, 2983, 2199, 1712, 1689, 1638, 1595, 1548, 1514, 1453, 1408, 1384, 1353, 1317, 1295, 1255, 1240, 1198, 974, 836, 813, 796 cm^{-1}. MS: *m*/*z* (%) = 378.00 (100) [M – 1]$^+$. $C_{20}H_{18}N_4O_2S$ (378.45): calcd. C 63.47, H 4.79, N 14.80; found C 63.45, H 5.08, N 14.51.

1b: White solid, 65%, m.p. 246–248 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.68 (br. s, 1 H, NH), 10.16 (br. s, 1 H, NH), 7.42 (d, J = 8.4 Hz, 2 H, ArH), 7.22–7.16 (m, 6 H, ArH, NH$_2$), 7.13 (d, J = 8.4 Hz, 2 H, ArH), 4.57 (d, J = 2.4 Hz, 1 H, CH), 4.17 (s, 1 H, CH), 2.30 (s, 3 H, CH$_3$), 2.26 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.3, 161.5, 150.5, 138.4, 136.7, 134.8, 132.9, 129.3, 129.2, 127.0, 119.8, 118.1, 70.6, 55.4, 51.3, 20.6, 20.3 ppm. IR (KBr): $\tilde{\nu}$ = 3431, 3304, 3192, 2987, 2202, 1714, 1691, 1639, 1591, 1551, 1513, 1409, 1383, 1350, 1318, 1294, 1241, 1197, 1109, 1023, 975, 887, 813, 798, 756 cm^{-1}. MS: *m*/*z* (%) = 391.58 (100) [M – 1]$^+$. $C_{21}H_{20}N_4O_2S$ (392.47): calcd. C 64.27, H 5.14, N 14.28; found C 64.12, H 5.43, N 14.45.

1c: White solid, 47%, m.p. >250 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.68 (br. s, 1 H, NH), 10.19 (br. s, 1 H, NH), 7.43 (d, J = 7.8 Hz, 2 H, ArH), 7.25 (s, 4 H, ArH), 7.18 (s, 2 H, NH$_2$), 7.14 (d, J = 7.8 Hz, 2 H, ArH), 4.59 (d, J = 3.0 Hz, 1 H, CH), 4.20 (s, 1 H, CH), 2.92–2.85 (m, 1 H, CH), 2.26 (s, 3 H, CH$_3$), 1.20 (d, J = 6.6 Hz, 6 H, CH$_3$) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.3, 161.5, 150.5, 147.4, 138.9, 134.9, 132.9, 129.3, 127.0, 126.6, 119.8, 118.2, 70.5, 55.3, 51.3, 33.1, 23.8, 20.4 ppm. IR (KBr): $\tilde{\nu}$ = 3436, 3363, 3296, 3231, 3187, 2959, 2203, 1711, 1686, 1638, 1594, 1550, 1510, 1410, 1315, 1237, 1194, 1053, 974, 815, 795 cm^{-1}. MS: *m*/*z* (%) = 419.71 (100) [M – 1]$^+$. $C_{23}H_{24}N_4O_2S$ (420.53): calcd. C 65.69, H 5.75, N 13.32; found C 65.84, H 5.90, N 13.11.

1d: White solid, 66%, m.p. 245–246 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.68 (br. s, 1 H, NH), 10.18 (br. s, 1 H, NH), 9.38 (s, 1 H, OH), 7.42 (d, J = 8.4 Hz, 2 H, ArH), 7.14–7.12 (m, 6 H, ArH, NH$_2$), 6.77 (d, J = 8.4 Hz, 2 H, ArH), 4.53 (d, J = 2.4 Hz, 1 H, CH), 4.15 (s, 1 H, CH), 2.26 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.4, 161.2, 156.8, 150.5, 134.8, 132.9, 131.6, 129.3, 128.1, 119.8, 118.2, 115.4, 71.0, 55.6, 51.2,

20.4 ppm. IR (KBr): ṽ = 3454, 3420, 3330, 3233, 3119, 2978, 2182, 1705, 1676, 1596, 1547, 1512, 1444, 1407, 1358, 1315, 1251, 1234, 1202, 1175, 1124, 1102, 970, 902, 821, 806, 791, 764 cm^{-1}. MS: *m*/*z* (%) = 393.56 (100) [M – 1]$^+$. $C_{20}H_{18}N_4O_3S$ (394.45): calcd. C 60.90, H 4.60, N 14.20; found C 60.85, H 4.77, N 14.05.

1e: White solid, 72%, m.p. 222–224 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.67 (br. s, 1 H, NH), 10.17 (br. s, 1 H, NH), 7.42 (d, *J* = 7.8 Hz, 2 H, ArH), 7.24 (d, *J* = 8.4 Hz, 2 H, ArH), 7.16–7.13 (m, 4 H, ArH, NH$_2$), 6.94 (d, *J* = 8.4 Hz, 2 H, ArH), 4.56 (s, 1 H, CH), 4.15 (s, 1 H, CH), 3.75 (s, 3 H, OCH$_3$), 2.26 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.3, 161.3, 158.7, 150.5, 134.8, 133.3, 132.8, 129.3, 128.2, 119.8, 118.2, 114.1, 70.8, 55.5, 55.1, 51.0, 20.3 ppm. IR (KBr): ṽ = 3343, 3303, 3135, 2977, 2195, 1705, 1671, 1600, 1547, 1509, 1409, 1349, 1301, 1232, 1194, 1175, 1031, 968, 820 cm^{-1}. MS: *m*/*z* (%) = 407.58 (100) [M – 1]$^+$. $C_{21}H_{20}N_4O_3S$ (408.47): calcd. C 61.75, H 4.94, N 13.72; found C 61.63, H 5.36, N 13.39.

1f: White solid, 51%, m.p. 244–246 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.78 (br. s, 1 H, NH), 10.26 (br. s, 1 H, NH), 7.43 (d, *J* = 7.2 Hz, 2 H, ArH), 7.39–7.37 (m, 2 H, ArH), 7.30 (s, 2 H, NH$_2$), 7.23 (t, *J* = 8.4 Hz, 2 H, ArH), 7.14 (d, *J* = 8.4 Hz, 2 H, ArH), 4.62 (d, *J* = 2.4 Hz, 1 H, CH), 4.12 (s, 1 H, CH), 2.27 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.2, 162.4, 161.8, 160.7, 150.5, 137.6, 134.9, 132.9, 129.3, 129.1, 129.0, 119.8, 118.1, 115.5, 115.4, 70.4, 55.4, 50.8, 20.3 ppm. IR (KBr): ṽ = 3424, 3326, 3228, 3159, 2971, 2188, 1719, 1681, 1623, 1597, 1575, 1544, 1503, 1408, 1384, 1349, 1314, 1256, 984, 885, 817, 789 cm^{-1}. MS: *m*/*z* (%) = 395.67 (100) [M – 1]$^+$. $C_{20}H_{17}FN_4O_2S$ (396.44): calcd. C 60.59, H 4.32, N 14.13; found C 60.44, H 4.69, N 13.86.

1g: White solid, 54%, m.p. 246–248 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.68 (br. s, 1 H, NH), 10.17 (br. s, 1 H, NH), 7.46–7.42 (m, 4 H, ArH), 7.37 (d, *J* = 8.4 Hz, 2 H, ArH), 7.26 (s, 2 H, NH$_2$), 7.14 (d, *J* = 8.4 Hz, 2 H, ArH), 4.63 (br. s, 1 H, CH), 4.19 (s, 1 H, CH), 2.27 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (150 MHz, [D$_6$]-DMSO): δ = 172.1, 162.0, 150.5, 140.4, 134.8, 132.9, 132.2, 129.3, 129.0, 128.7, 119.8, 118.0, 70.2, 55.2, 50.9, 20.4 ppm. IR (KBr): ṽ = 3408, 3314, 3192, 3136, 2983, 2889, 2208, 1893, 1713, 1687, 1660, 1599, 1555, 1514, 1489, 1409, 1359, 1316, 1297, 1241, 1191, 1122, 1088, 1014, 981, 937, 877, 816, 790, 761 cm^{-1}. MS: *m*/*z* (%) = 411.43 (100) [M – 1]$^+$, 413.38 (28) [M + 1]$^+$. $C_{20}H_{17}ClN_4O_2S$ (412.89): calcd. C 58.18, H 4.15, N 13.57; found C 57.70, H 4.36, N 13.29.

1h: White solid, 66%, m.p. 249–250 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.68 (br. s, 1 H, NH), 10.15 (br. s, 1 H, NH), 7.59 (d, *J* = 8.4 Hz, 2 H, ArH), 7.42 (d, *J* = 7.8 Hz, 2 H, ArH), 7.31 (d, *J* = 8.4 Hz, 2 H, ArH), 7.25 (s, 2 H, NH$_2$), 7.14 (d, *J* = 8.4 Hz, 2 H, ArH), 4.60 (d, *J* = 2.4 Hz, 1 H, CH), 4.18 (s, 1 H, CH), 2.26 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.1, 162.0, 150.5, 140.9, 134.8, 132.9, 131.6, 129.4, 129.3, 120.6, 119.8, 118.0, 70.0, 55.1, 51.0, 20.4 ppm. IR (KBr): ṽ = 3726, 3667, 3643, 3406, 3345, 3312, 3191, 3133, 2979, 2351, 2317, 2194, 1893, 1713, 1688, 1660, 1599, 1554, 1515, 1486, 1406, 1355, 1316, 1240, 1189, 1119, 1070, 1010, 979, 937, 879, 816, 790, 759 cm^{-1}. MS: *m*/*z* (%) = 455.39 (100) [M – 1]$^+$, 457.39 (97) [M + 1]$^+$. $C_{20}H_{17}BrN_4O_2S$ (457.34): calcd. C 52.52, H 3.75, N 12.25; found C 52.30, H 3.94, N 11.87.

1i: Yellow solid, 38%, m.p. >250 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.67 (br. s, 1 H, NH), 10.17 (br. s, 1 H, NH), 8.24 (br. s, 1 H, ArH), 8.20–8.18 (m, 1 H, ArH), 7.83 (d, *J* = 7.8 Hz, 1 H, ArH), 7.22 (t, *J* = 7.8 Hz, 1 H, ArH), 7.43 (d, *J* = 7.8 Hz, 2 H, ArH), 7.37 (s, 2 H, NH$_2$), 7.14 (d, *J* = 8.4 Hz, 2 H, ArH), 4.78 (br. s, 1 H, CH), 4.23 (br. s, 1 H, CH), 2.27 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.0, 162.7, 150.6, 148.1, 143.7, 134.9, 134.0, 132.9, 130.3, 129.3, 122.6, 121.9, 119.8, 117.9, 69.5, 55.1, 50.8, 20.3 ppm. IR (KBr): ṽ = 3435, 3311, 3234, 3205, 3129, 2980, 2200, 1712, 1691, 1650, 1598, 1555, 1525, 1408, 1351, 1241, 1188, 1121, 1099, 1081, 983, 932, 868, 814 cm^{-1}. MS: *m*/*z* (%) = 422.48 (100) [M – 1]$^+$. $C_{20}H_{17}N_5O_4S$ (423.45): calcd. C 56.73, H 4.05, N 16.54; found C 56.51, H 3.84, N 16.27.

General Procedure for the Preparation of Dihydrothiophenes by a One-Pot Four-Component Reaction of 1,3-Thiazolidinedione, Aromatic Aldehyde, Malononitrile, and Arylamine: A mixture of aromatic aldehyde (4.0 mmol), malononitrile (4.0 mmol, 0.264 g), and triethylamine (1.0 mmol, 0.101 g) in acetonitrile (5.0 mL) was stirred at room temperature for 2 min. Then arylamine (4.0 mmol) and 1,3-thiazolidinedione (4.0 mmol) were added and the reaction was stirred at 40 °C for an additional 48 h. The resulting precipitate was collected by filtration and washed with acetonitrile. The crude product was recrystallized with a mixture of acetonitrile and *N*,*N*-dimethylformamide to give the pure products **2a**–**2n**.

2a: White solid, 54%, m.p. 246–247 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.85 (br. s, 1 H, NH), 10.35 (br. s, 1 H, NH), 7.61 (d, *J* = 7.8 Hz, 2 H, ArH), 7.41–7.39 (m, 4 H, ArH), 7.35–7.30 (m, 3 H, ArH), 7.27 (s, 2 H, NH$_2$), 4.61 (d, *J* = 1.8 Hz, 1 H, CH), 4.17 (s, 1 H, CH) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.3, 161.7, 150.6, 141.5, 136.4, 128.7, 127.5, 127.1, 121.5, 118.1, 70.5, 55.3, 51.5 ppm. IR (KBr): ṽ = 3438, 3302, 3197, 3127, 2978, 2201, 1709, 1693, 1638, 1594, 1546, 1513, 1493, 1454, 1402, 1351, 1310, 1254, 1235, 1192, 1094, 1011, 973, 828, 767 cm^{-1}. MS: *m*/*z* (%) = 397.76 (100) [M – 1]$^+$, 399.49 (18) [M + 1]$^+$. $C_{19}H_{15}ClN_4O_2S$ (398.87): calcd. C 57.21, H 3.79, N 14.05; found C 57.53, H 4.27, N 13.70.

2b: White solid, 62%, m.p. 220–222 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.75 (br. s, 1 H, NH), 10.28 (br. s, 1 H, NH), 7.59 (d, *J* = 9.0 Hz, 2 H, ArH), 7.38 (d, *J* = 9.0 Hz, 2 H, ArH), 7.25 (d, *J* = 8.4 Hz, 2 H, ArH), 7.16 (s, 2 H, NH$_2$), 6.94 (d, *J* = 8.4 Hz, 2 H, ArH), 4.56 (d, *J* = 2.4 Hz, 1 H, CH), 4.15 (s, 1 H, CH), 3.75 (s, 3 H, OCH$_3$) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.3, 161.3, 158.7, 150.6, 136.4, 133.3, 128.7, 128.2, 127.5, 121.5, 118.2, 114.1, 70.8, 55.5, 55.1, 51.0 ppm. IR (KBr): ṽ = 3424, 3336, 3302, 3228, 3143, 2964, 2837, 2179, 1716, 1678, 1633, 1594, 1570, 1539, 1494, 1402, 1357, 1334, 1307, 1252, 1217, 1180, 1116, 1093, 1027, 978, 884, 823, 791, 752 cm^{-1}. MS: *m*/*z* (%) = 427.67 (100) [M – 1]$^+$, 429.62 (37) [M + 1]$^+$. $C_{20}H_{17}ClN_4O_3S$ (428.89): calcd. C 56.01, H 4.00, N 13.06; found C 55.74, H 4.28, N 12.75.

2c: Yellow solid, 57%, m.p. 232–234 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.74 (br. s, 1 H, NH), 10.27 (br. s, 1 H, NH), 7.60 (d, *J* = 8.4 Hz, 2 H, ArH), 7.39–7.37 (m, 4 H, ArH), 7.23–7.20 (m, 4 H, ArH, NH$_2$), 4.62 (br. s, 1 H, CH), 4.18 (s, 1 H, CH) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.2, 162.4, 161.8, 160.7, 150.6, 137.5, 136.4, 129.1, 129.0, 128.7, 127.5, 121.4, 118.1, 115.5, 115.4, 70.4, 55.4, 50.8 ppm. IR (KBr): ṽ = 3455, 3346, 3303, 3233, 3119, 2982, 2191, 1705, 1672, 1594, 1548, 1513, 1401, 1354, 1306, 1250, 1230, 1210, 1117, 1092, 1011, 971, 938, 905, 830, 804, 766 cm^{-1}. MS: *m*/*z* (%) = 415.34 (100) [M – 1]$^+$. $C_{19}H_{14}ClFN_4O_2S$ (416.86): calcd. C 54.74, H 3.39, N 13.44; found C 54.90, H 3.56, N 13.07.

2d: White solid, 67%, m.p. 233–234 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.75 (br. s, 1 H, NH), 10.27 (br. s, 1 H, NH), 7.60 (d, *J* = 8.4 Hz, 2 H, ArH), 7.46 (d, *J* = 8.4 Hz, 2 H, ArH), 7.38 (d, *J* = 7.8 Hz, 4 H, ArH), 7.25 (s, 2 H, NH$_2$), 4.62 (br. s, 1 H, CH), 4.18 (s, 1 H, CH) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.1, 162.0, 150.6, 140.4, 136.4, 132.2, 129.0, 128.7, 128.6, 127.6, 121.4, 118.0, 70.1, 55.2, 50.9 ppm. IR (KBr): ṽ = 3390, 3305, 3222, 3156, 2964, 2179, 1709, 1692, 1633, 1595, 1552, 1490, 1403, 1359, 1302, 1280, 1217, 1180, 1088, 1011, 975, 886, 822, 766 cm^{-1}. MS:

m/z (%) = 431.38 (100) $[M - 1]^+$, 433.36 (81) $[M + 1]^+$. $C_{19}H_{14}Cl_2N_4O_2S$ (433.31): calcd. C 52.67, H 4.26, N 12.93; found C 52.49, H 3.52, N 12.66.

2e: Yellow solid, 44%, m.p. 247–250 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.75 (br. s, 1 H, NH), 10.28 (br. s, 1 H, NH), 8.25 (s, 1 H, ArH), 8.20–8.19 (m, 1 H, ArH), 7.83 (d, *J* = 7.8 Hz, 1 H, ArH), 7.72 (t, *J* = 7.8 Hz, 1 H, ArH), 7.61 (d, *J* = 9.0 Hz, 2 H, ArH), 7.40–7.38 (m, 4 H, ArH, NH_2), 4.79 (s, 1 H, CH), 4.24 (s, 1 H, CH) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.0, 162.7, 150.6, 148.1, 143.7, 136.4, 134.0, 130.3, 128.7, 127.5, 122.6, 121.9, 121.4, 117.9, 69.5, 55.1, 50.7 ppm. IR (KBr): $\tilde{\nu}$ = 3437, 3310, 3233, 3129, 2980, 2200, 1715, 1692, 1649, 1596, 1552, 1525, 1492, 1403, 1350, 1307, 1255, 1235, 1187, 1095, 1010, 981, 931, 828, 807, 773, 751 cm^{-1}. MS: *m/z* (%) = 442.66 (100) $[M - 1]^+$. $C_{19}H_{14}ClN_5O_4S$ (443.86): calcd. C 51.41, H 3.18, N 15.78; found C 51.28, H 3.65, N 15.49.

2f: White solid, 50%, m.p. 244–246 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.81 (br. s, 1 H, NH), 10.33 (br. s, 1 H, NH), 7.55 (d, *J* = 7.8 Hz, 2 H, ArH), 7.40 (t, *J* = 7.2 Hz, 2 H, ArH), 7.35–7.30 (m, 5 H, ArH), 7.27 (s, 2 H, NH_2), 7.10 (t, *J* = 7.2 Hz, 1 H, ArH), 4.61 (d, *J* = 2.4 Hz, 1 H, CH), 4.17 (s, 1 H, CH) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.3, 161.7, 150.5, 141.5, 137.4, 128.9, 128.7, 127.5, 127.1, 123.8, 119.8, 118.2, 70.5, 55.3, 51.6 ppm. IR (KBr): $\tilde{\nu}$ = 3432, 3300, 3188, 2989, 2200, 1716, 1699, 1638, 1592, 1551, 1524, 1448, 1384, 1350, 1329, 1256, 1201, 1079, 993, 973, 889, 837, 775, 756 cm^{-1}. MS: *m/z* (%) = 363.40 (100) $[M - 1]^+$. $C_{19}H_{16}N_4O_2S$ (364.42): calcd. C 62.62, H 4.43, N 15.37; found C 62.48, H 4.72, N 15.04.

2g: Light-yellow solid, 80%, m.p. 217–219 °C. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 10.71 (br. s, 1 H, NH), 10.24 (br. s, 1 H, NH), 7.54 (d, *J* = 7.8 Hz, 2 H, ArH), 7.33 (t, *J* = 7.8 Hz, 2 H, ArH), 7.25 (d, *J* = 8.4 Hz, 2 H, ArH), 7.16 (s, 2 H, NH_2), 7.10 (t, *J* = 7.2 Hz, 1 H, ArH), 6.95 (d, *J* = 8.4 Hz, 2 H, ArH), 4.57 (d, *J* = 2.4 Hz, 1 H, CH), 4.16 (s, 1 H, CH), 3.75 (s, 3 H, OCH_3) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 171.3, 160.3, 157.6, 149.4, 136.3, 132.2, 127.8, 127.1, 122.7, 118.7, 117.1, 116.8, 113.0, 69.7, 54.5, 54.0, 50.0 ppm. IR (KBr): $\tilde{\nu}$ = 3403, 3342, 3303, 3200, 2996, 2836, 2245, 2190, 1713, 1636, 1591, 1562, 1509, 1476, 1448, 1356, 1309, 1259, 1224, 1160, 1111, 1084, 1031, 979, 887, 828, 790, 761 cm^{-1}. MS: *m/z* (%) = 393.75 (100) $[M - 1]^+$. $C_{20}H_{18}N_4O_3S$ (394.45): calcd. C 60.90, H 4.60, N 14.20; found C 60.66, H 4.83, N 13.87.

2h: White solid, 75%, m.p. 248–250 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.81 (br. s, 1 H, NH), 10.34 (br. s, 1 H, NH), 7.56 (d, *J* = 7.2 Hz, 2 H, ArH), 7.47 (d, *J* = 8.4 Hz, 2 H, ArH), 7.38 (d, *J* = 8.4 Hz, 2 H, ArH), 7.36–7.33 (m, 4 H, ArH, NH_2), 7.10 (t, *J* = 7.2 Hz, 1 H, ArH), 4.62 (br. s, 1 H, CH), 4.15 (s, 1 H, CH) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.2, 162.0, 150.5, 140.4, 137.4, 132.1, 129.0, 128.9, 128.7, 123.8, 119.8, 118.0, 70.1, 55.2, 50.9 ppm. IR (KBr): $\tilde{\nu}$ = 3457, 3298, 3226, 3186, 2990, 2200, 1690, 1641, 1587, 1560, 1495, 1446, 1410, 1384, 1344, 1326, 1313, 1242, 1203, 1178, 1089, 1030, 1014, 990, 977, 900, 884, 827, 799, 768, 753 cm^{-1}. MS: *m/z* (%) = 397.57 $[M - 1]^+$, 419.46 (100) $[M - 1 + Na]^+$, 421.50 (30) $[M + 1 + Na]^+$. $C_{19}H_{15}ClN_4O_2S$ (398.87): calcd. C 57.21, H 3.79, N 14.05; found C 57.16, H 4.05, N 13.72.

2i: White solid, 79%, m.p. >250 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.71 (br. s, 1 H, NH), 10.22 (br. s, 1 H, NH), 7.59 (d, *J* = 8.4 Hz, 2 H, ArH), 7.54 (d, *J* = 7.8 Hz, 2 H, ArH), 7.35–7.31 (m, 4 H, ArH), 7.26 (s, 2 H, NH_2), 7.10 (t, *J* = 7.8 Hz, 1 H, ArH), 4.61 (d, *J* = 1.8 Hz, 1 H, CH), 4.19 (s, 1 H, CH) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.1, 162.0, 150.5, 140.9, 137.4, 131.6, 129.4, 128.9, 123.8, 120.6, 119.8, 118.0, 70.0, 55.1, 50.9 ppm. IR (KBr): $\tilde{\nu}$ = 3458, 3297, 3186, 2991, 2199, 1692, 1640, 1586, 1560, 1497, 1446, 1407, 1384, 1346, 1326, 1313, 1243, 1202, 1178, 1073, 1010, 977, 900, 883, 824, 765, 753 cm^{-1}. MS: *m/z* (%) = 441.53 (100) $[M - 1]^+$, 443.61 (98) $[M + 1]^+$. $C_{19}H_{15}BrN_4O_2S$ (443.32): calcd. C 51.48, H 3.41, N 12.64; found C 51.33, H 3.79, N 12.42.

2j: White solid, 60%, m.p. 210–212 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 11.04 (s, 2 H, NH), 8.09 (d, *J* = 6.6 Hz, 1 H, ArH), 8.00–7.99 (m, 2 H, ArH), 7.76 (d, *J* = 7.8 Hz, 1 H, ArH), 7.71 (t, *J* = 7.8 Hz, 1 H, ArH), 7.61 (t, *J* = 7.2 Hz, 1 H, ArH), 7.53 (t, *J* = 7.8 Hz, 1 H, ArH), 7.30–7.27 (m, 4 H, ArH, NH_2), 6.97–6.96 (m, 2 H, ArH), 4.65 (d, *J* = 2.4 Hz, 1 H, CH), 4.19 (s, 1 H, CH), 3.76 (s, 3 H, OCH_3) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 173.1, 161.4, 158.7, 151.0, 133.6, 133.4, 132.4, 128.6, 128.2, 126.7, 126.2, 125.8, 125.6, 124.5, 120.4, 118.3, 118.2, 114.1, 70.9, 55.6, 55.1, 51.1 ppm. IR (KBr): $\tilde{\nu}$ = 3431, 3302, 3198, 2972, 2191, 1710, 1632, 1566, 1510, 1405, 1349, 1304, 1250, 1177, 1031, 987, 794, 770 cm^{-1}. MS: *m/z* (%) = 443.64 (100) $[M - 1]^+$. $C_{24}H_{20}N_4O_3S$ (444.51): calcd. C 64.85, H 4.54, N 12.60; found C 64.57, H 4.80, N 12.35.

2k: White solid, 78%, m.p. 206–208 °C. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 10.98 (s, 1 H, NH), 10.83 (s, 1 H, NH), 8.24 (d, *J* = 8.4 Hz, 1 H, ArH), 7.54 (d, *J* = 7.2 Hz, 1 H, ArH), 7.35 (t, *J* = 7.8 Hz, 1 H, ArH), 7.26 (d, *J* = 8.4 Hz, 2 H, ArH), 7.17–7.13 (m, 3 H, ArH, NH_2), 6.95 (d, *J* = 8.4 Hz, 2 H, ArH), 4.57 (d, *J* = 2.4 Hz, 1 H, CH), 4.15 (s, 1 H, CH), 3.76 (s, 3 H, OCH_3) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.8, 161.3, 158.7, 150.5, 134.5, 133.3, 129.3, 128.2, 127.8, 124.8, 122.4, 121.3, 118.2, 114.1, 70.8, 55.5, 55.1, 51.0 ppm. IR (KBr): $\tilde{\nu}$ = 3442, 3310, 3202, 2195, 1710, 1676, 1643, 1583, 1537, 1511, 1462, 1361, 1289, 1247, 1215, 1177, 1062, 1033, 973, 887, 828 cm^{-1}. MS: *m/z* (%) = 427.59 (100) $[M - 1]^+$, 429.42 (39) $[M + 1]^+$. $C_{20}H_{17}ClN_4O_3S$ (428.89): calcd. C 56.01, H 4.00, N 13.06; found C 56.37, H 4.29, N 12.77.

2l: White solid, 56%, m.p. 225–228 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.79 (s, 1 H, NH), 10.33 (s, 1 H, NH), 7.79 (s, 1 H, ArH), 7.44 (d, *J* = 8.4 Hz, 1 H, ArH), 7.35 (t, *J* = 8.4 Hz, 1 H, ArH), 7.25 (d, *J* = 8.4 Hz, 2 H, ArH), 7.17–7.15 (m, 3 H, ArH, NH_2), 6.95 (d, *J* = 9.0 Hz, 2 H, ArH), 4.57 (d, *J* = 2.4 Hz, 1 H, CH), 4.17 (s, 1 H, CH), 3.76 (s, 3 H, OCH_3) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.3, 161.3, 158.7, 150.6, 138.9, 133.2, 130.4, 128.2, 123.5, 119.4, 118.3, 118.2, 114.1, 70.8, 55.6, 55.1, 51.0 ppm. IR (KBr): $\tilde{\nu}$ = 3453, 3306, 3195, 3139, 2986, 2194, 1693, 1640, 1590, 1554, 1508, 1477, 1424, 1348, 1321, 1301, 1278, 1249, 1174, 1105, 1077, 1036, 983, 883, 826, 777 cm^{-1}. MS: *m/z* (%) = 427.32 (100) $[M - 1]^+$, 429.31 (29) $[M + 1]^+$. $C_{20}H_{17}ClN_4O_3S$ (428.89): calcd. C 56.01, H 4.00, N 13.06; found C 55.82, H 4.43, N 12.69.

2m: White solid, 57%, m.p. 222–224 °C. ^{1}H NMR (600 MHz, [D$_6$] DMSO): δ = 11.05 (s, 1 H, NH), 10.87 (s, 1 H, NH), 8.26 (d, *J* = 9.0 Hz, 1 H, ArH), 7.71 (d, *J* = 2.4 Hz, 1 H, ArH), 7.45–7.43 (m, 1 H, ArH), 7.26 (d, *J* = 9.0 Hz, 2 H, ArH), 7.18 (s, 2 H, NH_2), 6.94 (d, *J* = 8.4 Hz, 2 H, ArH), 4.56 (d, *J* = 3.0 Hz, 1 H, CH), 4.15 (s, 1 H, CH), 3.76 (s, 3 H, OCH_3) ppm. ^{13}C NMR (150 MHz, [D$_6$]-DMSO): δ = 172.9, 161.3, 158.7, 150.5, 133.7, 133.3, 128.7, 128.2, 127.9, 127.8, 123.3, 122.2, 118.2, 114.1, 70.8, 55.4, 55.1, 51.0 ppm. IR (KBr): $\tilde{\nu}$ = 3434, 3329, 3228, 3160, 2970, 2838, 2180, 1712, 1682, 1631, 1583, 1536, 1500, 1388, 1346, 1300, 1250, 1219, 1178, 1100, 1061, 1031, 982, 885, 860, 814, 758 cm^{-1}. MS: *m/z* (%) = 461.48 (100) $[M - 1]^+$, 463.51 (34) $[M + 1]^+$. $C_{20}H_{16}Cl_2N_4O_3S$ (463.34): calcd. C 51.84, H 3.48, N 12.09; found C 51.79, H 3.50, N 11.69.

2n: Yellow solid, 28%, m.p. 218–220 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.90 (s, 1 H, NH), 10.64 (s, 1 H, NH), 8.22 (d, *J* =

8.4 Hz, 2 H, ArH), 7.84 (d, J = 8.4 Hz, 2 H, ArH), 7.25 (d, J = 8.4 Hz, 2 H, ArH), 7.17 (s, 2 H, NH_2), 6.95 (d, J = 8.4 Hz, 2 H, ArH), 4.57 (s, 1 H, CH), 4.17 (s, 1 H, CH), 3.76 (s, 3 H, OCH_3) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 172.4, 161.3, 158.7, 150.6, 143.8, 142.7, 133.2, 128.2, 124.9, 119.6, 118.2, 114.1, 70.8, 55.6, 55.1, 50.9 ppm. IR (KBr): $\tilde{\nu}$ = 3449, 3326, 3124, 2972, 2195, 1705, 1630, 1557, 1416, 1338, 1310, 1267, 1236, 1169, 1112, 1028, 884, 850, 815, 744 cm^{-1}. MS: m/z (%) = 438.51 (100) [M – 1]$^+$. $C_{20}H_{17}N_5O_5S$ (439.44): calcd. C 54.66, H 3.90, N 15.94; found C 54.50, H 4.13, N 15.78.

General Procedure for the Preparation of Thiophenes by the Dehydrogenation of Dihydrothiophenes: A suspension of dihydrothiophene (2.0 mmol) and DDQ (2.4 mmol, 0.545 g) in acetonitrile (10 mL) was stirred at 35–40 °C for about 2–4 h. The resulting precipitate was filtered and washed with acetonitrile to give to give the pure products **3a**–**3e**.

3a: White solid, 93%, m.p. >250 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.26 (s, 1 H, NH), 9.19 (s, 1 H, NH), 8.20 (s, 2 H, NH_2), 7.60 (d, J = 8.4 Hz, 2 H, ArH), 7.50–7.46 (m, 4 H, ArH), 7.30 (t, J = 7.2 Hz, 2 H, ArH), 7.07 (t, J = 7.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 167.6, 162.4, 150.5, 145.2, 137.9, 134.7, 131.9, 131.5, 129.3, 129.2, 124.2, 120.1, 115.2, 112.1, 89.1 ppm. IR (KBr): $\tilde{\nu}$ = 3374, 3295, 3203, 2216, 1691, 1632, 1597, 1557, 1526, 1501, 1472, 1443, 1413, 1304, 1256, 1225, 1152, 1088, 1014, 890, 833, 753 cm^{-1}. MS: m/z (%) = 395.67 (100) [M – 1]$^+$, 397.57 (46) [M + 1]$^+$. $C_{19}H_{13}ClN_4O_2S$ (396.85): calcd. C 57.50, H 3.30, N 14.12; found C 57.42, H 3.68, N 13.75.

3b: White solid, 95%, m.p. >250 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.28 (s, 1 H, NH), 9.19 (s, 1 H, NH), 8.15 (s, 2 H, NH_2), 7.58 (d, J = 8.4 Hz, 2 H, ArH), 7.51–7.47 (m, 4 H, ArH), 7.34 (d, J = 9.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (150 MHz, [D$_6$]-DMSO): δ = 167.6, 162.4, 150.6, 145.4, 136.9, 134.6, 131.9, 131.5, 129.2, 127.9, 121.8, 115.2, 111.9, 89.1 ppm. IR (KBr): $\tilde{\nu}$ = 3452, 3311, 3215, 2214, 1729, 1637, 1551, 1501, 1478, 1403, 1311, 1264, 1216, 1094, 1011, 820, 743 cm^{-1}. MS: m/z (%) = 429.71 (100) [M – 1]$^+$, 431.44 (70) [M + 1$^+$]. $C_{19}H_{12}Cl_2N_4O_2S$ (431.30): calcd. C 52.91, H 2.80, N 12.99; found C 52.76, H 3.28, N 12.66.

3c: Light-yellow solid, 94%, m.p. >250 °C. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 10.16 (s, 1 H, NH), 9.05 (s, 1 H, NH), 8.13 (s, 2 H, NH_2), 7.72 (d, J = 8.4 Hz, 2 H, ArH), 7.41 (d, J = 8.4 Hz, 2 H, ArH), 7.33 (d, J = 8.4 Hz, 2 H, ArH), 7.10 (d, J = 8.4 Hz, 2 H, ArH), 2.24 (s, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 167.5, 162.4, 150.4, 145.2, 135.3, 133.2, 132.3, 131.8, 129.7, 123.3, 120.2, 115.2, 112.0, 88.9, 20.8 ppm. IR (KBr): $\tilde{\nu}$ = 3458, 3317, 3213, 2213, 1702, 1628, 1594, 1550, 1521, 1472, 1408, 1306, 1261, 1216, 1169, 811, 757 cm^{-1}. MS: m/z (%) = 453.58 (100) [M – 1]$^+$, 455.50 (98) [M + 1]$^+$. $C_{20}H_{15}BrN_4O_2S$ (455.33): calcd. C 52.76, H 3.32, N 12.30; found C 52.55, H 3.51, N 12.04.

3d: White solid, 95%, m.p. >250 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.27 (s, 1 H, NH), 9.23 (s, 1 H, NH), 8.19 (s, 2 H, NH_2), 7.73 (d, J = 8.4 Hz, 2 H, ArH), 7.47 (d, J = 8.4 Hz, 2 H, ArH), 7.4.2 (d, J = 8.4 Hz, 2 H, ArH), 7.30 (t, J = 7.8 Hz, 2 H, ArH), 7.07 (t, J = 7.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 167.6, 162.4, 150.5, 145.3, 137.9, 132.3, 132.2, 131.8, 129.3, 124.2, 123.4, 120.2, 115.2, 112.0, 89.0 ppm. IR (KBr): $\tilde{\nu}$ = 3375, 3296, 3204, 2216, 1691, 1659, 1632, 1597, 1557, 1526, 1500, 1472, 1443, 1413, 1386, 1305, 1256, 1226, 1153, 1085, 1011, 890, 833, 753 cm^{-1}. MS: m/z (%) = 439.66 (100) [M – 1]$^+$, 441.58 (98) [M + 1]$^+$. $C_{19}H_{13}BrN_4O_2S$ (441.30): calcd. C 51.71, H 2.97, N 12.70; found C 51.64, H 3.22, N 12.48.

3e: Yellow solid, 90%, m.p. 242–243 °C. ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 10.22 (s, 1 H, NH), 9.90 (s, 1 H, NH), 8.34–8.32 (m, 1 H, ArH), 8.26 (t, J = 1.8 Hz, 1 H, ArH), 8.24 (s, 2 H, NH_2), 7.91 (d, J = 7.8 Hz, 1 H, ArH), 7.78 (t, J = 7.8 Hz, 1 H, ArH), 7.49 (d, J = 9.0 Hz, 2 H, ArH), 7.34 (d, J = 9.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 167.5, 162.4, 150.8, 147.9, 144.2, 137.0, 136.5, 134.9, 130.5, 129.1, 128.9, 127.8, 124.5, 124.2, 121.8, 115.7, 115.2, 112.5, 88.7 ppm. IR (KBr): $\tilde{\nu}$ = 3440, 3329, 3247, 2216, 1724, 1633, 1596, 1481, 1405, 1350, 1318, 1265, 1218, 1181, 1097, 828, 735 cm^{-1}. MS: m/z (%) = 440.88 (100) [M – 1]$^+$, 442.66 (41) [M + 1]$^+$. $C_{19}H_{12}ClN_5O_4S$ (441.85): calcd. C 51.65, H 2.74, N 15.85; found C 51.27, H 3.03, N 15.49.

CCDC-727666 (for **1e**), -727669 (for **2c**), -727672 (for **2f**), -727667 (for **2i**), -727670 (for **2j**), -727671 (for **2l**) and -727668 (for **3e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (Grant No. 20672091).

[1] a) J. Zhu, H. Bienaym, *Multicomponent Reactions*, Wiley-VCH, Weinheim, **2005**; b) L. F. Tiestze, G. Brasche, K. F. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

[2] a) D. J. Ramón, M. Yus, *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634; b) A. Domling, *Chem. Rev.* **2006**, *106*, 17–89.

[3] a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210.

[4] a) D. J. Vugts, M. M. Koningstein, R. F. Schmitz, F. J. J. de Kanter, M. B. Groen, R. V. A. Orru, *Chem. Eur. J.* **2006**, *12*, 7178–7189; b) T. E. Nielsen, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2008**, *47*, 48–56.

[5] a) D. M. D′Souza, T. J. J. Mueller, *Chem. Soc. Rev.* **2007**, *36*, 1095–1108; b) G. Guillena, D. J. Ramon, M. Yus, *Tetrahedron: Asymmetry* **2007**, *18*, 693–700; c) A. Padwa, S. K. Bur, *Tetrahedron* **2007**, *63*, 5341–5378.

[6] a) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal, *Acc. Chem. Res.* **2003**, *36*, 899–907; b) A. Dondoni, A. Massi, *Acc. Chem. Res.* **2006**, *39*, 451–463; c) S. L. Schreiber, *Science* **2000**, *287*, 1964–1969.

[7] a) A. T. Khan, T. Parvin, L. H. Choudhury, *J. Org. Chem.* **2008**, *73*, 8398–8402; b) S. Benetti, R. Romagnoli, C. De Risi, G. Spalluto, V. Zanirato, *Chem. Rev.* **1995**, *95*, 1065–1114; c) P. Langer, *Synthesis* **2002**, 441–459.

[8] a) C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.* **2004**, 4957–4980; b) F. Li, T. Muller, C. Simon, T. Constantieux, J. Rodriguez, *QSAR Comb. Sci.* **2006**, *25*, 432–438.

[9] a) R. Orru, M. de Greef, *Synthesis* **2003**, 1471–1499; b) H. Fujioka, K. Murai, O. Kubo, Y. Ohba, Y. Kita, *Org. Lett.* **2007**, *9*, 1687–1690; c) C. G. Yan, X. K. Song, Q. F. Wang, U. Siemeling, C. Bruhn, *Chem. Commun.* **2008**, 1440–1442.

[10] a) V. S. Matiychuk, R. B. Lesyk, M. O. Obushak, A. Gzella, D. V. Atamanyuk, Y. V. Ostapiuk, A. P. Kryshchyshyn, *Tetrahedron Lett.* **2008**, *49*, 4648–4651; b) L. F. Tietze, T. Pfeiffer, A. Schuffenhauer, *Eur. J. Org. Chem.* **1998**, *12*, 2733–2741.

[11] a) N. D. Sonawane, A. S. Verkman, *Bioorg. Med. Chem.* **2008**, *16*, 8187–8195; b) A. Verma, S. K. Saraf, *Eur. J. Med. Chem.* **2008**, *43*, 897–905.

[12] B. Fábián, V. Kudar, A. Csámpai, T. Z. Nagy, P. Sohár, *J. Organomet. Chem.* **2007**, *692*, 5621–5632.

[13] M. Maccari, R. Ottanà, C. Curinga, M. G. Vigorita, D. Rakowitz, T. Steindl, T. Langer, *Bioorg. Med. Chem.* **2005**, *13*, 2809–2823.

[14] J. Sun, L. L. Zhang, E. Y. Xia, C. G. Yan, *J. Org. Chem.* **2009**, *74*, 3398–3401.

[15] a) N. N. Sauer, R. J. Angelici, Y. C. J. Huang, W. S. Trahanovsky, *J. Org. Chem.* **1986**, *51*, 113–114; b) J. M. McIntosh, J. M. Masse, *J. Org. Chem.* **1975**, *40*, 1294–1298; c) M. Avalos, R. Babiano, A. Cabanillas, P. Cintas, *J. Org. Chem.* **1996**, *61*, 3738–3748.

[16] a) M. Hanédanian, O. Loreau, F. Taran, C. Mioskowski, *Tetrahedron Lett.* **2004**, *45*, 7035–7038; b) M. Hamaguchi, N. Funakoshi, T. Oshima, *Tetrahedron Lett.* **1999**, *40*, 8117–8120.

[17] S. M. Yang, J. M. Fang, *Tetrahedron* **2007**, *63*, 1421–1428.

Received: July 26, 2009
Published Online: September 15, 2009

