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One-pot synthesis of new tetrasubstituted thiophenes and selenophenes

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ABSTRACT

In this work, we described the synthesis of new tetrasubstituted thiophenes and selenophenes achieved by an easy one-pot four-step procedure. Expected compounds were obtained in good yield from ketene dithioacetals.

1. Introduction

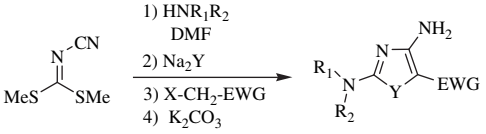
Thiophene is a major scaffold in heterocyclic chemistry, found in many compounds.[1] Moreover some of them have interesting properties. It has been showed that they inhibit the growth of *Escherichia coli*, *Micrococcus luteus*, and *Aspergillus niger*.[2] *N*-(5-Substituted)-thiophene-2-alkylsulfonamides are potent inhibitors for 5-lipoxygenase.[3] Thienopyridinones are good inhibitors of NMDA (*N*-methyl-D-aspartate) receptor.[4] Also, 3-amino-2-nitrobenzo[*b*]thiophene was used as starting material for the preparation of dyes.[5]

One major field of investigation of our team is the synthesis of heterocyclic compounds with potential biological activity.[6] Recently, we described the preparation of 2,4,5-trisubstituted-1,3-thiazoles and selenazoles from dimethyl cyanodithioimidocarbonate using a one-pot four-step procedure (Scheme 1).[7]

In this work, we extended these methods to access to new tetrasubstituted thiophenes and selenophenes from ketene dithioacetals.

2. Results and discussion

Ketene dithioacetals are versatile starting materials for many heterocyclic products.[8–12] At the laboratory, these compounds, used for the preparation of thiophenes and thieno-condensed systems,[9] were prepared from malonitrile successfully reacted with a base, an isothiocyanate, and an activated halide.[9a,10] Few years ago, this method was optimized using ketene *N*,*S*-acetals as intermediate (Scheme 2).[9a–c] Another possibility to obtain thiophenes substituted by a secondary amine is to realize an S_NAr reaction on substituted 2-methylsulfanylthiophenes (Scheme 2).[11,12]



Y = S, Se
X = Cl, Br
EWG= CN, CO_2Et, Ac, NO_2, Bz, *p*-Cl-C_6H_4-CO

Scheme 1. Synthesis of 2,4,5-trisubstituted-1,3-thiazoles and selenazoles.

In this work, we propose an alternative route using ketene dithioacetals as starting material. The first step of our strategy was the preparation of ketene dithioacetals **1**,**2**, respectively, from malononitrile and 2,4-pentanedione. The expected compounds **1**,**2** were obtained easily in high yield as reported in literature (Scheme 3).[9]

Inspired by the methodology we established recently to prepare 2,4,5-trisubstituted thiazoles from dimethyl cyanodithioimidocarbonate (Scheme 1),[7] we have presumed that compounds **3**–**8**

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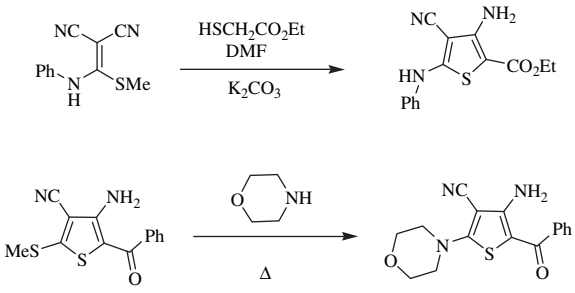
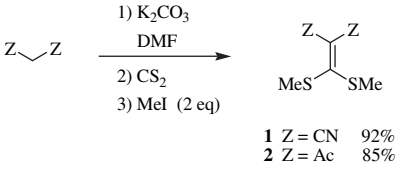
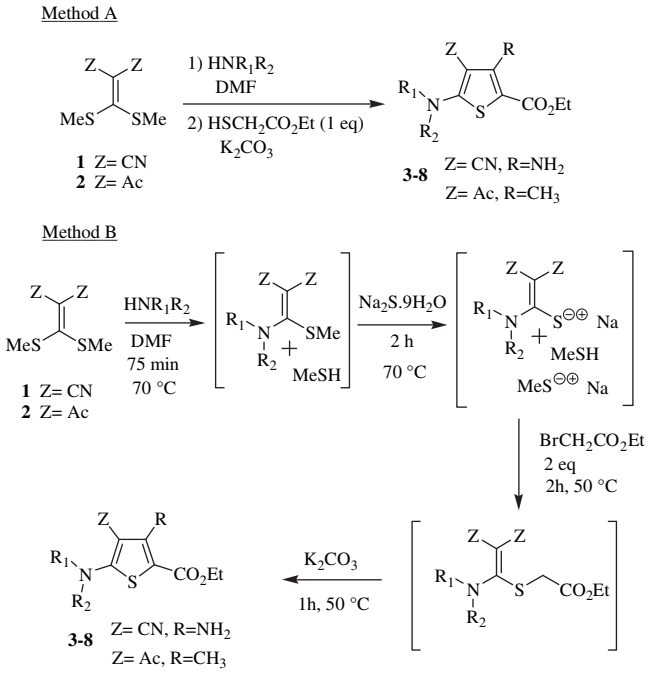


Scheme 2. Two examples of the synthesis of substituted 2-aminothiophenes in literature.



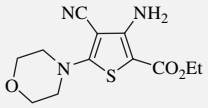
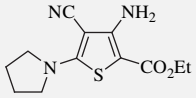
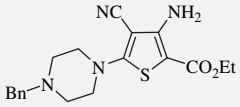
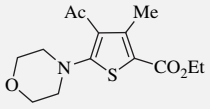
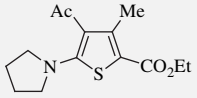
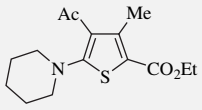
Scheme 3. Synthesis of ketene dithioacetals.

could be obtained directly from ketene dithioacetals **1**–**2**. We used a sequential procedure (Method A, Scheme 4). Compounds **1**–**2** were dissolved in DMF, then the secondary amine was added and heated at 70 °C for 75 min. After this time, ethyl thioglycolate and potassium carbonate were successively added and heated for 3 h. Expected compounds were obtained in yields ranging from 17% to 80% (Table 1). Ethyl thioglycolate may also be replaced by sodium sulfide and ethyl bromoacetate (Method B, Scheme 4). After the formation of the intermediate ketene *N*,*S*-acetals, sodium sulfide was added to form the intermediate thiolate liberating 1 equiv of methyl thiolate in the reaction media. The first equivalent of ethyl bromoacetate was consumed by the methyl thiolate so that 2 equiv of the activated halide were required. Finally, potassium carbonate was added to perform the cyclization (Method B, Scheme 4). Compounds **3**–**8** were obtained in better yields (31–90%) than using Method A because sodium sulfide is more nucleophilic than ethyl thioglycolate (Table 1).

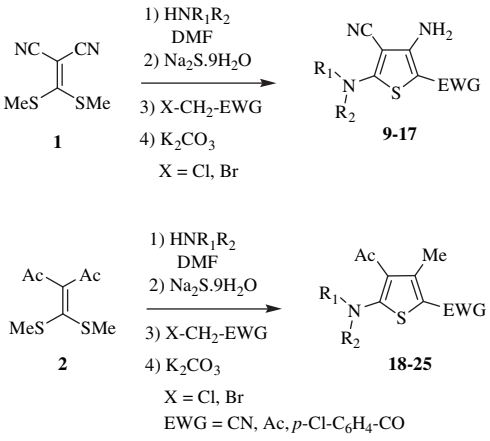


Scheme 4. Synthesis of substituted ethyl-2-thiophenecarboxylates **3**–**8**.

Table 1
Synthesis of substituted ethyl-2-thiophenecarboxylates **3**–**8**, comparison of Methods A and B

Compound	Entry	Method A	Method B
	**3**	28%	43%
	**4**	80%	77%
	**5**	40%	50%
	**6**	63%	31%
	**7**	17%	90%
	**8**	19%	62%

Moreover sodium sulfide allowed us to extend this method to activated halides like chloroacetonitrile, chloracetone, and ω-bromo-*p*-chloroacetophenone and diversify the substitution of thiophenes in position 5 (Scheme 5).



Scheme 5. One-pot four-step synthesis of polysubstituted thiophenes.

Substituted 3-aminothiophenes **9**–**17** and substituted 3-methylthiophenes **18**–**25** were synthesized, respectively, from **1** and **2** in good yields. In all cases, the best results were obtained adding 2 equiv of the activated halide (Tables 2 and 3).

In comparison with literature, this one-pot four-step procedure presents some improvements and advantages. The yields that we obtained are good and this method is one-step shorter than the S_NAr way. In terms of construction of the thiophene ring, this strategy is elegant and effective. In the same reaction, substitution on positions 2 and 5 was determined choosing the appropriate secondary amine and activated halide. Moreover substitution on positions 3 and 4 was determined choosing the appropriate ketene

Table 2
Synthesis of substituted 3-aminothiophenes **9**–**17**

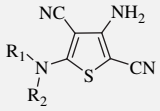
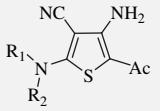
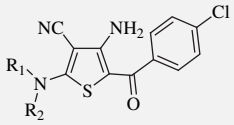
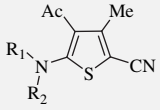
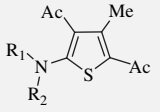
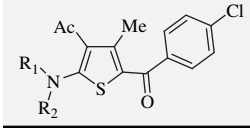
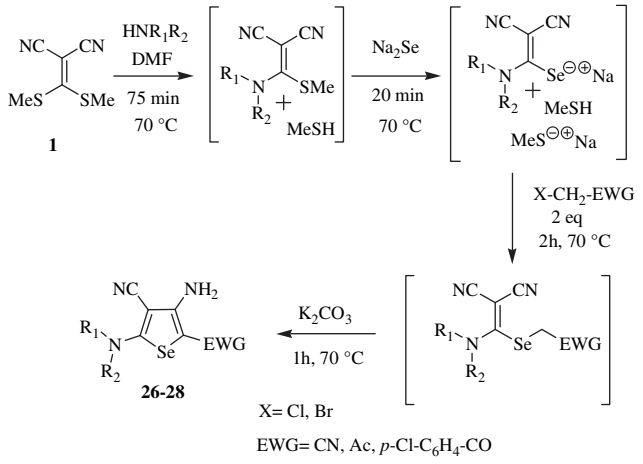
Compound	–NR_1R_2	Halide used X–CH_2–EWG	Entry	Yield (%)
	4-Morpholinyl-	Chloroacetonitrile (2 equiv)	**9**	74
	1-Pyrrolidinyl-		**10**	74
	4-Benzyl-1-piperazinyl-		**11**	63
	4-Morpholinyl-	Chloroacetone (2 equiv)	**12**	77
	1-Pyrrolidinyl-		**13**	90
	4-Benzyl-1-piperazinyl-		**14**	73
	4-Morpholinyl-	ω-Bromo-*p*-chloroacetophenone (2 equiv)	**15**	60
	1-Pyrrolidinyl-		**16**	80
	4-Benzyl-1-piperazinyl-		**17**	71

Table 3
Synthesis of substituted 3-methylthiophenes **18**–**25**

Compound	–NR_1R_2	Halide used X–CH_2–EWG	Entry	Yield (%)
	4-Morpholinyl-	Chloroacetonitrile (2 equiv)	**18**	44
	1-Pyrrolidinyl-		**19**	37
	1-Piperidinyl-		**20**	64
	4-Morpholinyl-	Chloroacetone (2 equiv)	**21**	55
	1-Pyrrolidinyl-		**22**	67
	1-Piperidinyl-		**23**	65
	4-Morpholinyl-	ω-Bromo-*p*-chloroacetophenone (2 equiv)	**24**	92
	1-Piperidinyl-		**25**	48

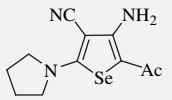
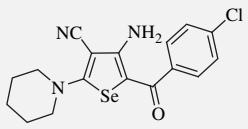
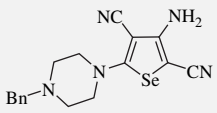
dithioacetals as starting material. We extend this one-pot four-step procedure using sodium selenide instead of sodium sulfide to access to new tetrasubstituted selenophenes.

Compound **1** was heated at 70 °C during 1 h with a secondary amine to form the first intermediate (Scheme 6). Sodium selenide was prepared freshly,[13] filtered under an argon atmosphere, and added to the reaction mixture at 70 °C to form the intermediate selenolate. After 20 min, the activated halide (2 equiv) was added dropwise and stirred for two more hours. Cyclization was performed by addition of potassium carbonate (Scheme 6). Pouring the reaction mixture in water gave the compounds **26**–**28** as solids in moderate to good yields (Table 4). As for the preparation of thiophenes **3**–**17**, we had to use 2 equiv of activated halide to isolate tetrasubstituted selenophenes **26**–**28**. We tried to prepare substituted 3-methylselenophenes from compound **2** using this one-pot four-step procedure but unfortunately the expected compounds could not be isolated. But it was not really a surprise because in literature, the synthesis of selenophenes from ketene *N*,*S*-acetal 3-[anilino(methylsulfanyl)methylene]-2,4-pentanedione was unsuccessful.[14]



Scheme 6. Synthesis of substituted 3-aminoselenophenes: one-pot four-step sequential procedure.

Table 4
Synthesis of substituted 3-aminoselenophenes **26**–**29**

Compound	Halide used X–CH_2–EWG	Yield (%)
 **26**	Chloroacetone (2 equiv)	88
 **27**	ω-Bromo-*p*-chloroacetophenone (2 equiv)	38
 **28**	Chloroacetonitrile (2 equiv)	19

3. Conclusion

Here we demonstrated that our sequential procedure is very convenient for the synthesis of tetrasubstituted thiophenes and trisubstituted 3-aminoselenophenes. We determined the conditions to obtain expected compounds in good yields. This method is shorter than the S_NAr pathway. Another advantage is that ketene dithioacetals **1** and **2** were the same starting material for the preparation of all thiophenes and selenophenes.

4. Experimental section

4.1. General

Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. IR spectra were performed on a Perkin–Elmer FT-IR Baragon 1000PC equipped with a Graseby-Specac golden gate and treated with the Spectrum (Perkin–Elmer) software version 5.3.1. ^{1}H and ^{13}C NMR spectra (δ in ppm) were recorded on an AC Bruker 250 MHz spectrometer in $CDCl_3$ or DMSO-d_6. MS spectra were recorded on an Agilent Technologies GC–MS instrument equipped with a 7683 injector, 6890 N gas chromatograph and a 5973 mass selective detector. The mass spectrometer was operated in EI mode at 70 eV and MS spectra were recorded from m/z 50 to 650. HMRS were collected on a Bruker MICROTOF-Q ESI/QqTOF spectrometer.

4.2. Synthesis of 2-[bis(methylsulfanyl)methylene]-malononitrile (1)

0.2 mol of malononitrile was dissolved in DMF (240 mL). Potassium carbonate (0.2 mol) was added and the solution was stirred for 2 h at room temperature. Carbon disulfide was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Methyl iodide (0.4 mol) was added dropwise at 0 °C and the reaction was stirred at room temperature for 3 h. The precipitate was filtered and the solid was washed with water and dried at room temperature until constant weight. The compound was used without further purification for the synthesis of thiophenes and selenophenes. Only a small portion of the solid was purified by recrystallization in isopropanol.

Yield: 92%. Colorless solid; mp 82 °C; mp_{lit}[15]: 80–81 °C. IR: 2176 (s) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.75 (s, 6H, 2×CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 19.3, 74.4, 112.7, 185.8.

4.3. Synthesis of 3-[bis(methylsulfanyl)methylene]-2,4-pentanedione (2)

0.2 mol of 2,4-pentanedione was dissolved in DMF (240 mL). Potassium carbonate (0.2 mol) was added and the solution was stirred for 2 h at room temperature. Carbon disulfide was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Methyl iodide (0.4 mol) was added dropwise at 0 °C and the reaction was stirred at room temperature for 24 h. The precipitate was filtered and the solid was washed with water and dried at room temperature until constant weight. The compound was used without further purification for the synthesis of thiophenes and selenophenes. Only a small portion of the solid was purified by recrystallization in isopropanol.

Yield: 85%. Colorless solid; mp 61 °C; mp_{lit}[16]: 61 °C. IR: 2176 (s) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.37 (s, 6H, 2×CH_3); 2.40 (s, 6H, 2×CH_3). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 18.5, 30.8, 144.5, 152.8, 197.6.

4.4. Synthesis of substituted 3-amino-4-cyanothiophenes

4.4.1. General Method.

4.4.1.1. Method A. 2-[Bis(methylsulfanyl)methylene]malononitrile **1** or 3-[bis(methylsulfanyl)methylene]-2,4-pentanedione **2** (0.01 mol) was dissolved in DMF (15 mL). The secondary amine (0.01 mol) was added and the mixture was heated at 70 °C for 75 min. Then ethyl thioglycolate (0.01 mol) and potassium carbonate (0.01 mol) were added and heated for 2 h at 70 °C. The mixture was poured onto water (100 mL) with good stirring. The precipitate was filtered, washed with water, and dried at room temperature until constant weight and purified by recrystallization in ethanol.

4.4.1.2. Method B. 2-[Bis(methylsulfanyl)methylene)malononitrile **1** or 3-[bis(methylsulfanyl]methylene]-2,4-pentanedione **2** (0.01 mol) was dissolved in DMF (15 mL). The secondary amine (0.01 mol) was added and the mixture was heated at 70 °C for 75 min. Then, $Na_2S\cdot 9H_2O$ (0.01 mol) was added and heated for 2 h at 70 °C. The activated halide (0.02 mol) was added dropwise at 70 °C. The mixture was heated at 70 °C for 2 h and the potassium carbonate was added (0.02 mol). The reaction was stirred at 70 °C for 90 min more. The mixture was poured onto water (100 mL) with good stirring. When a precipitate appeared, it was filtered, washed with water, and dried at room temperature until constant weight. When a viscous mixture appeared, 25 mL of ether was added and the precipitate was filtered, washed with water, and dried at room temperature until constant weight. The isolated solid was purified by recrystallization in ethanol or acetonitrile.

*4.4.2. Ethyl 3-amino-4-cyano-5-(4-morpholinyl)-2-thiophenecarboxylate (**3**).* Yield: 28% (Method A), 43% (Method B). Colorless solid; mp 133 °C. IR: 3343 (s), 3312 (s), 2200 (s), 1655 (s) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.20 (t, J=7.5 Hz, 3H, CH_3), 3.54 (m, 4H, 2×CH_2), 3.71 (m, 4H, 2×CH_2), 4.12 (q, J=7.2 Hz, 2H, CH_2), 5.65 (s, 2H, NH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 14.4, 49.6, 59.3, 65.0, 77.9, 115.2, 135.1, 155.3, 162.7, 166.6. GC–MS (EI, 70 eV): m/z (%): 281 (100), 253 (33), 236 (20), 209 (36), 195 (14), 177 (18), 151 (9). HRMS calcd for $C_{12}H_{16}N_3O_3S$ $[M+H]^+$ 282.0907, found 282.0894.

*4.4.3. Ethyl 3-amino-4-cyano-5-(1-pyrrolidinyl)-2-thiophenecarboxylate (**4**).* Yield: 80% (Method A), 77% (Method B). Colorless solid; mp 215 °C. IR: 3421 (s), 3319 (s), 2199 (s), 1645 (s) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.27 (t, J=7.5 Hz, 3H, CH_3), 2.05 (m, 4H, 2×CH_2), 3.59 (m, 4H, 2×CH_2), 4.19 (q, J=7.5 Hz, 2H, CH_2), 6.68 (s, 2H, NH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 14.5, 25.2, 51.2, 59.0, 75.0, 115.9, 162.1, 162.7, 169.4, 170.5. GC–MS (EI, 70 eV): m/z (%): 265 (100), 237 (37), 220 (27), 193 (48). HRMS calcd for $C_{12}H_{16}N_3O_2S$ $[M+H]^+$ 266.0958, found 266.0949.

*4.4.4. Ethyl 3-amino-5-(4-benzyl-1-piperazinyl)-4-cyano-2-thiophenecarboxylate (**5**).* Yield: 40% (Method A), 50% (Method B). Colorless solid; mp 122 °C. IR: 3440 (s), 3335 (s), 2196 (s), 1660 (s) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.30 (t, J=7.5 Hz, 3H, CH_3), 2.60 (m, 4H, 2×CH_2), 3.54 (s, 2H, CH_2), 3.63 (m, 3H), 3.83 (m, 1H), 4.23 (q, J=7.5 Hz, 2H, CH_2), 5.81 (s, 2H, NH_2), 7.37 (m, 5H, 5×CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 14.4, 49.8, 51.3, 59.2, 77.7, 115.3, 127.1, 128.4, 129.2, 137.4, 162.7, 166.1, 169.4, 175.3, 177.6. GC–MS (EI, 70 eV): m/z (%): 370 (100), 325 (11), 279 (19), 209 (13), 91 (90). HRMS calcd for $C_{19}H_{23}N_4O_2S$ $[M+H]^+$ 371.1536, found 371.1515.

*4.4.5. Ethyl 4-acetyl-3-methyl-5-(4-morpholinyl)-2-thiophenecarboxylate (**6**).* Yield: 63% (Method A), 31% (Method B). Yellow solid; mp 137–138 °C. IR: 2984 (s), 1698 (s), 1661 (s) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.35 (t, J=7.2 Hz, 3H, CH_3), 2.48 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.08 (m, 4H, 2×CH_2), 3.84 (m, 4H, 2×CH_2), 4.28 (q, J=7.2 Hz,

2H, CH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 14.7, 15.8, 29.7, 54.0, 60.6, 66.0, 116.5, 129.8, 145.8, 162.4, 164.7, 198.4. GC–MS (EI, 70 eV): *m*/*z* (%): 297 (100), 280 (57), 252 (25), 197 (26). HRMS calcd for $C_{14}H_{20}NO_4S$ $[M+H]^+$ 298.1108, found 298.1096.

*4.4.6. Ethyl 4-acetyl-3-methyl-5-(1-pyrrolidinyl)-2-thiophenecarboxylate (**7**).* Yield: 17% (Method A), 90% (Method B). Pale brown solid; mp 103–104 °C. IR: 2962 (s), 1683 (s), 1646 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.33 (t, *J*=7.1 Hz, 3H, CH_3), 2.00 (m, 4H, 2×CH_2), 2.51 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.21 (m, 4H, 2×CH_2), 4.26 (q, *J*=7.1 Hz, 2H, CH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 14.5, 15.5, 25.8, 31.9, 53.0, 60.2, 109.3, 122.2, 145.9, 160.7, 162.9, 198.2. GC–MS (EI, 70 eV): *m*/*z* (%): 281 (100), 266 (36), 238 (29), 197 (28), 70 (16). HRMS calcd for $C_{14}H_{20}NO_3S$ $[M+H]^+$ 282,1158, found 282.1157.

*4.4.7. Ethyl 4-acetyl-3-methyl-5-(4-piperidinyl)-2-thiophenecarboxylate (**8**).* Yield: 19% (Method A), 62% (Method B). Yellow solid; mp 69–70 °C. IR: 2938 (s), 1693 (s), 1667 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.31 (t, *J*=7.5 Hz, 3H, CH_3), 1.63 (m, 4H, 2×CH_2), 1.71 (m, 2H, CH_2), 2.51 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.06 (m, 4H, 2×CH_2), 4.26 (q, *J*=7.5 Hz, 2H, CH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 14.4, 14.8, 23.5, 25.4, 29.2, 56.0, 60.5, 114.9, 128.4, 146.2, 162.7, 166.7, 198.7. GC–MS (EI, 70 eV): *m*/*z* (%): 295 (100), 278 (94), 250 (27), 205 (26), 82 (23). HRMS calcd for $C_{15}H_{22}NO_3S$ $[M+H]^+$ 296.1315, found 296.1317.

*4.4.8. 3-Amino-5-(4-morpholinyl)-2,4-thiophenedicarbonitrile (**9**).* Yield: 74% (Method B). Colorless solid; mp 277 °C. IR: 3414 (m), 3339 (s), 3237 (s), 2200 (m), 2177 (s), 1643 (m) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 3.51 (m, 4H, 2×CH_2), 3.71 (m, 4H, 2×CH_2), 6.64 (s, 2H, NH_2). ^{13}C NMR (250 MHz, DMSO-d_6): δ 49.6, 60.5, 65.0, 77.7, 114.8, 115.4, 157.0, 166.4. GC–MS (EI, 70 eV): *m*/*z* (%): 234 (100), 176 (60). HRMS calcd for $C_{10}H_{11}N_4OS$ $[M+H]^+$ 235.0648, found 235.0645.

*4.4.9. 3-Amino-5-(1-pyrrolidinyl)-2,4-thiophenedicarbonitrile (**10**).* Yield: 74%. Colorless solid; mp 206 °C. IR: 3387 (s), 3330 (s), 3225 (s), 2176 (s), 1648 (m), 1534 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.96 (m, 4H, 2×CH_2), 3.50 (m, 4H, 2×CH_2), 6.52 (s, 2H, NH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 25.2, 51.3, 74.5, 83.4, 115.5, 115.9, 157.3, 161.8. GC–MS (EI, 70 eV): *m*/*z* (%): 218 (100), 190 (14), 176 (22). HRMS calcd for $C_{10}H_{11}N_4S$ $[M+H]^+$ 219.0699, found 219.0689.

*4.4.10. 3-Amino-5-(4-benzyl-1-piperazinyl)-2,4-thiophenedicarbonitrile (**11**).* Yield: 63%. Brown solid; mp 181 °C. IR: 3377 (s), 3335 (s), 3234 (s), 2182 (s), 1653 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 2.47 (m, 4H, 2×CH_2), 3.31 (s, 2H, CH_2), 3.55 (m, 4H, 2×CH_2), 6.61 (s, 2H, NH_2), 7.27 (m, 5H, 5×CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 49.9, 51.2, 60.3, 61.4, 77.6, 114.8, 115.4, 127.1, 128.2, 128.9, 137.4, 157.0, 165.9. GC–MS (EI, 70 eV): *m*/*z* (%): 323 (75), 232 (21), 91 (100), 56 (15). HRMS calcd for $C_{17}H_{18}N_5S$ $[M+H]^+$ 324.1277, found 324.1259.

*4.4.11. 5-Acetyl-4-amino-2-(4-morpholinyl)-3-thiophenecarbonitrile (**12**).* Yield: 77% (Method B). Colorless solid; mp 244 °C (dec). IR: 3408 (s), 3305 (s), 2196 (s), 1595 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 2.09 (s, 3H, CH_3), 3.58 (m, 4H, 2×CH_2), 3.73 (m, 4H, 2×CH_2), 7.47 (s, 2H, NH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 27.8, 49.7, 65.0, 77.5, 115.1, 128.6, 130.8, 166.2, 186.3. GC–MS (EI, 70 eV): *m*/*z* (%): 251 (100), 236 (87), 208 (15), 193 (10), 178 (37). HRMS calcd for $C_{11}H_{14}N_3O_2S$ $[M+H]^+$ 252.0801, found 252.0802.

*4.4.12. 5-Acetyl-4-amino-2-(1-pyrrolidinyl)-3-thiophenecarbonitrile (**13**).* Yield: 90%. Orange solid; mp 254 °C (dec). IR: 3375 (m), 3285 (m), 2949 (m), 2196 (s), 1586 (s), 1621 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.98 (m, 4H, 2×CH_2), 2.05 (s, 3H, CH_3), 3.58 (m, 4H, 2×CH_2), 7.54 (s, 2H, NH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 22.0, 28.4, 57.7, 83.7, 111.8, 116.9, 122.0, 127.1, 204.5. GC–MS (EI, 70 eV): *m*/*z* (%): 235 (77), 220 (100), 192 (34), 167 (30), 70 (14). HRMS calcd for $C_{11}H_{14}N_3OS$ $[M+H]^+$ 236.0852, found 236.0862.

*4.4.13. 5-Acetyl-4-amino-2-(4-benzyl-1-piperazinyl)-3-thiophenecarbonitrile (**14**).* Yield: 73%. Orange solid; mp 192 °C. IR: 3376 (s), 3288 (s), 3191 (s), 2195 (s), 1623 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 2.07 (s, 3H, CH_3), 2.52 (m, 4H, 2×CH_2), 3.52 (s, 2H, CH_2), 3.61 (m, 4H, 2×CH_2), 7.31 (m, 5H, 5×CH), 7.47 (s, 2H, NH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 49.9, 51.2, 60.3, 61.4, 77.6, 114.8, 115.4, 127.1, 128.2, 128.9, 137.4, 157.0, 166.0. GC–MS (EI, 70 eV): *m*/*z* (%): 340 (100), 269 (14), 249 (21), 91 (100), 56 (19). HRMS calcd for $C_{18}H_{21}N_4OS$ $[M+H]^+$ 341.1431, found 341.1418.

*4.4.14. 4-Amino-5-(4-chlorobenzoyl)-2-(4-morpholinyl)-3-thiophenecarbonitrile (**15**).* Yield: 60% (Method B). Yellow solid; mp 236 °C. IR: 3371 (s), 3350 (s), 3233 (s), 2198 (s), 1650 (m), 1587 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 3.58 (m, 4H, 2×CH_2), 3.70 (m, 4H, 2×CH_2), 7.51 (d, *J*=8.3 Hz, 2H, 2×CH), 7.61 (d, *J*=8.3 Hz, 2H, 2×CH), 7.96 (s, 2H, NH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 49.7, 65.0, 77.1, 93.5, 115.0, 128.6, 128.7, 135.2, 139.4, 159.1, 167.5, 182.6. GC–MS (EI, 70 eV): *m*/*z* (%): 347 (100), 288 (34), 261 (15), 236 (8), 208 (5). HRMS calcd for $C_{16}H_{15}N_3O_2SCl$ $[M+H]^+$ 348.0568, found 348.0549.

*4.4.15. 4-Amino-5-(4-chlorobenzoyl)-2-(1-pyrrolidinyl)-3-thiophenecarbonitrile (**16**).* Yield: 80% (Method B). Yellow solid; mp 231 °C. IR: 3427 (m), 3269 (m), 2196 (s), 1555 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.96 (m, 4H, 2×CH_2), 3.55 (m, 4H, 2×CH_2), 7.52 (d, *J*=8.3 Hz, 2H, 2×CH), 7.60 (d, *J*=8.3 Hz, 2H, 2×CH), 7.98 (s, 2H, NH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 21.6, 51.5, 75.5, 93.2, 115.5, 128.5, 128.6, 135.0, 139.7, 159.5, 163.4, 181.8. GC–MS (EI, 70 eV): *m*/*z* (%): 331 (100), 261 (15), 139 (21), 111 (20). HRMS calcd for $C_{16}H_{15}N_3OSCl$ $[M+H]^+$ 332.0619, found 332.0597.

*4.4.16. 4-Amino-2-(4-benzyl-1-piperazinyl)-5-(4-chlorobenzoyl)-3-thiophenecarbonitrile (**17**).* Yield: 71%. Yellow crystal; mp 186 °C. IR: 3387 (s), 3279 (s), 2202 (s), 1584 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 2.57 (m, 4H, 2×CH_2), 3.59 (s, 2H, CH_2), 3.70 (m, 4H, 2×CH_2), 7.38 (m, 5H, 5×CH), 7.60 (d, *J*=8.3 Hz, 2H, 2×CH), 7.69 (d, *J*=8.3 Hz, 2H, 2×CH), 8.05 (s, 2H, NH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 50.0, 51.3, 61.3, 77.0, 93.4, 115.0, 127.1, 128.2, 128.5, 128.7, 128.9, 129.1, 135.2, 139.5, 159.2, 167.1, 182.5. GC–MS (EI, 70 eV): *m*/*z* (%): 307 (100), 292 (10), 197 (12), 139 (23), 111 (25), 75 (13). HRMS calcd for $C_{23}H_{22}N_4OSCl$ $[M+H]^+$ 437.1197, found 437.1187.

*4.4.17. 4-Acetyl-3-methyl-5-(4-morpholinyl)-2-thiophenecarbonitrile (**18**).* Yield: 44%. Pale brown crystal; mp 148 °C. IR: 2916 (s), 2202 (s), 1656 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.09 (m, 4H, 2×CH_2), 3.86 (m, 4H, 2×CH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 18.8, 31.0, 51.5, 66.5, 103.5, 113.5. 135.0, 149.9, 159.5, 193.1. GC–MS (EI, 70 eV): *m*/*z* (%): 250 (100), 233 (71), 219 (14), 192 (35), 177 (50), 164 (39), 150 (45). HRMS calcd for $C_{12}H_{15}N_2O_2S$ $[M+H]^+$ 251.0849, found 251.0846.

*4.4.18. 4-Acetyl-3-methyl-5-(1-pyrrolidinyl)-2-thiophenecarbonitrile (**19**).* Yield: 37%. Brown crystal; mp 100–101 °C. IR: 2919 (m), 2193 (s), 1662 (s), 1639 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.97 (m, 4H, 2×CH_2), 2.36 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.15 (m, 4H, 2×CH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 17.1, 26.0, 31.3, 54.2, 115.6, 119.6, 143.2, 149.1, 162.3, 195.6. GC–MS (EI, 70 eV): *m*/*z* (%): 234 (100), 217 (33), 201 (13), 191 (53), 178 (20), 150 (46), 70 (42). HRMS calcd for $C_{12}H_{15}N_2OS$ $[M+H]^+$ 235.0900, found 235.0902.

*4.4.19. 4-Acetyl-3-methyl-5-(4-piperidinyl)-2-thiophenecarbonitrile (**20**).* Yield: 64%. Brown crystal; mp 118–119 °C. IR: 2928 (s), 2200

(s), 1668 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.55 (m, 2H, CH_2), 1.68 (m, 4H, 2×CH_2), 2.31 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.00 (m, 4H, 2×CH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 14.8, 23.3, 24.9, 28.7, 56.0, 93.8, 114.7, 126.1, 150.2, 168.3, 196.6. GC–MS (EI, 70 eV): *m*/*z* (%): 248 (80), 231 (100), 83 (23), 55 (14). HRMS calcd for $C_{13}H_{17}N_2OS$ $[M+H]^+$ 249.1056, found 249.1046.

*4.4.20. 2,4-Diacetyl-3-methyl-5-(4-morpholinyl)-2-thiophene (**21**).* Yield: 55%. Pale brown crystal; mp 92–93 °C. IR: 2971 (s), 1675 (s), 1642 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 2.46 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.10 (m, 4H, 2×CH_2), 3.84 (m, 4H, 2×CH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 16.4, 18.8, 26.9, 29.9, 31.4, 134.6, 139.1, 144.4, 155.3, 190.1, 195.7. GC–MS (EI, 70 eV): *m*/*z* (%): 267 (100), 252 (67), 208 (27), 194 (49), 167 (33). HRMS calcd for $C_{13}H_{18}NO_3S$ $[M+H]^+$ 268.1002, found 268.0992.

*4.4.21. 2,4-Diacetyl-3-methyl-5-(1-pyrrolidinyl)-2-thiophene (**22**).* Yield: 67%. Yellow crystal; mp 120–121 °C. IR: 2969 (m), 1666 (m), 1621 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 2.00 (m, 4H, 2×CH_2), 2.38 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.24 (m, 4H, 2×CH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 16.2, 25.8, 29.7, 32.3, 53.4 120.7, 122.9, 144.5, 160.3, 189.4, 199.2. GC–MS (EI, 70 eV): *m*/*z* (%): 251 (100), 236 (49), 208 (39), 167 (30), 70 (14). HRMS calcd for $C_{13}H_{18}NO_2S$ $[M+H]^+$ 252.1053, found 252.1049.

*4.4.22. 2,4-Diacetyl-3-methyl-5-(4-piperidinyl)-2-thiophene (**23**).* Yield: 65%. Colorless crystal; mp 112–113 °C. IR: 2916 (m), 1686 (m), 1634 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.53 (m, 2H, CH_2), 1.66 (m, 4H, 2×CH_2), 2.38 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.03 (m, 4H, 2×CH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 15.5, 23.5, 24.9, 29.9, 30.2, 56.5, 125.3, 128.6, 144.7, 166.4, 190.3, 199.1. GC–MS (EI, 70 eV): *m*/*z* (%): 211 (52), 196 (100), 181 (12), 124 (15), 83 (14), 69 (4).

*4.4.23. 3-Acetyl-5-(4-chlorobenzoyl)-4-methyl-2-(4-morpholinyl)-3-thiophene (**24**).* Yield: 92%. Yellow crystal; mp 188 °C. IR: 2957 (s), 1662 (s), 1625 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 2.22 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.04 (m, 4H, 2×CH_2), 3.78 (m, 4H, 2×CH_2), 7.37 (d, *J*=8.6 Hz, 2H, 2×CH), 7.63 (d, *J*=8.6 Hz, 2H, 2×CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 16.7, 29.8, 54.5, 66.1, 125.3, 128.6, 129.7, 130.0, 138.3, 138.4, 145.2, 165.9, 187.9, 198.5. GC–MS (EI, 70 eV): *m*/*z* (%): 363 (100), 348 (48), 304 (23), 263 (16), 139 (81), 111 (36). HRMS calcd for $C_{18}H_{19}NO_3SCl$ $[M+H]^+$ 364.0769, found 364.0760.

*4.4.24. 3-Acetyl-5-(4-Chlorobenzoyl)-4-methyl-2-(4-piperidinyl)-3-thiophene (**25**).* Yield: 48%. Yellow solid; mp 137 °C. IR: 2930 (s), 1666 (s), 1618 (s), 1585 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.50 (m, 2H, CH_2), 1.61 (m, 4H, 2×CH_2), 2.16 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.05 (m, 4H, 2×CH_2), 7.53 (d, *J*=8.5 Hz, 2H, 2×CH), 7.64 (d, *J*=8.5 Hz, 2H, 2×CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 16.0, 22.8, 24.7, 29.1, 55.1, 122.0, 127.0, 128.5, 130.0, 136.4, 138.9, 145.4, 166.9, 186.7, 197.9. GC–MS (EI, 70 eV): *m*/*z* (%): 361 (100), 346 (66), 318 (6). HRMS calcd for $C_{19}H_{21}NO_2SCl$ $[M+H]^+$ 362.0976, found 362.0961.

4.5. Synthesis of substituted 4-amino-3-cyanoselenophenes: general procedure

2-[Bis(methylsulfanyl)methylene]malononitrile **1** (0.01 mol) was dissolved in DMF (15 mL). The secondary amine (0.01 mol) was added and the mixture was heated at 70 °C for 75 min. Then, fresh sodium selenide (0.01 mol) was added and heated for 20 min at 70 °C. Activated halide (0.02–0.03 mol) was added dropwise at 70 °C. The mixture was heated at 70 °C for 2 h and the potassium carbonate was added (0.01 mol). The reaction was stirred at 70 °C for 1 h more. The mixture was poured onto water (100 mL) with good stirring. The precipitate was filtered, washed with water, and dried at room temperature until constant weight. The isolated solid was purified by recrystallization in acetonitrile.

No satisfying ^{13}C NMR spectra were obtained for these three compounds: due to their very low solubility, recording ^{13}C NMR spectra required long time accumulation and those products were not stable in solution for a long time.

*4.5.1. 5-Acetyl-4-amino-2-(1-pyrrolidinyl)-3-selenophenecarbonitrile (**26**).* Yield: 88%. Brown solid; mp 279 °C. IR: 3340 (s), 3270 (s), 3171 (s), 2955 (m), 2193 (s), 1623 (s), 1577 (s), 1540 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 2.01 (m, 7H, 2×CH_2+CH_3), 3.57 (m, 4H, 2×CH_2), 7.61 (s, 2H, NH_2). GC–MS (EI, 70 eV): *m*/*z* (%): 283 (74), 268 (100), 240 (22). HRMS calcd for $C_{11}H_{14}N_3OSe$ $[M+H]^+$ 284.0297, found 284.0280.

*4.5.2. 4-Amino-5-(4-chlorobenzoyl)-2-(1-piperidinyl)-3-selenophenecarbonitrile (**27**).* Yield: 38%. Brown solid; mp 177 °C. IR: 3397 (s), 3260 (s), 2952 (m), 2194 (s), 1580 (s), 1538 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.62 (m, 6H, 3×CH_2), 3.63 (m, 4H, 2×CH_2), 7.55 (m, 4H, 4×CH), 7.97 (s, 2H, NH_2). GC–MS (EI, 70 eV): *m*/*z* (%): 393 (100), 336 (8), 309 (15), 282 (14), 254 (11). HRMS calcd for $C_{17}H_{17}N_3OSe$ $[M+H]^+$ 394.0218, found 394.0195.

*4.5.3. 3-Amino-5-(4-benzyl-1-piperazinyl)-2,4-selenophenedicarbonitrile (**28**).* Yield: 19%. Yellow solid; mp 158 °C. IR: 3388 (s), 3328 (s), 3230 (s), 2172 (s), 1644 (s), 1550 (s), 1520 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 2.60 (m, 4H, 2×CH_2), 3.63 (m, 6H, 2×CH_2+CH_2), 4.79 (s, 2H, NH_2), 7.30 (m, 5H, 5×CH). GC–MS (EI, 70 eV): *m*/*z* (%): 371 (41), 280 (10), 262 (8). HRMS calcd for $C_{17}H_{18}N_5Se$ $[M+H]^+$ 372.0723, found 372.0696.

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