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One-pot synthesis of new 2,4,5-trisubstituted 1,3-thiazoles and 1,3-selenazoles

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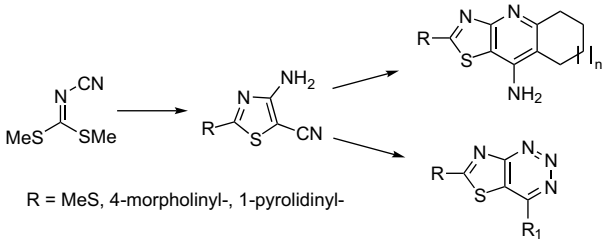
ABSTRACT

In this work, we describe the synthesis of new 2,4,5-trisubstituted-1,3-thiazoles and 1,3-selenazole achieved by an easy one-pot four-step procedure. Expected compounds were obtained in good yield from dimethyl cyanodithioimidocarbonate, which was the common starting material for the preparation of all 1,3-thiazoles and 1,3-selenazoles. Chemical diversity was introduced on thiazole and selenazole rings by varying the amines and the activated halides used.

1. Introduction

Thiazole is an important scaffold in heterocyclic chemistry and 1,3-thiazole ring is present in many pharmacological active substances.[1] For example thiazole-5-ylacetic acid derivatives have strong anti-inflammatory activity.[2] It has also been shown that 1,3-benzothiazoles derivatives are histamine H_3 antagonists.[3] Imidazo[2,1-*b*]thiazole moiety has versatile biological properties depending on the substituents. Substituted by a 2,4,6-trichlorophenyl group, this compound has herbicidal activity.[4] Imidazo[2,1-*b*]thiazole guanylhydrazones showed antitumoral activity.[5] Recently, imidazo[2,1-*b*]thiazoles substituted by dihydropyridines showed selective cardiodepressant activity.[6]

One major field of investigation of our team is the synthesis of heterocyclic compounds with potential biological activity.[7] In a previous work, we described the synthesis of thiazolopyridines and thiazolotriazines from substituted 4-amino-1,3-thiazole-5-carbonitriles (Scheme 1).[8] These useful starting materials were prepared by a new sequential reaction from dimethyl cyanodithioimidocarbonate. In this work, we extended this method to five activated halides and we have optimized the conditions to obtain new substituted 3-amino-1,3-thiazoles and selenazoles.



Scheme 1. Synthesis of thiazolopyridines and thiazolotriazines.

2. Results and discussion

There are many pathways to synthesize substituted 2-amino-1,3-thiazoles. Thiourea is a convenient starting material to prepare 2-amino-1,3-thiazoles.[9] For 1,3-thiazoles substituted by a primary amine in position 2, Gewald et al. used cyanamide, an isothiocyanate, and an activated halide.[10] Another efficient strategy is to choose amidino-thiourea as starting material.[1a,11] 1,3-Oxathiolium cation can afford 1,3-thiazoles substituted in position 2 by a secondary amine but it is not the easiest way to obtain this class of compounds.[2b] S_NAr reactions with secondary amine on 2-(methylsulfanyl)-1,3-thiazole derivatives are well described.[3,12]

In a previous work,[8] we took advantage of the good leaving group property of the methylsulfanyl group of 4-amino-2-(methylsulfanyl)-1,3-thiazole-5-carbonitrile **2**. Our synthesis began with the preparation of dimethyl cyanodithioimidocarbonate **1** from cyanamide as described in the literature.[13] Compound **1** was

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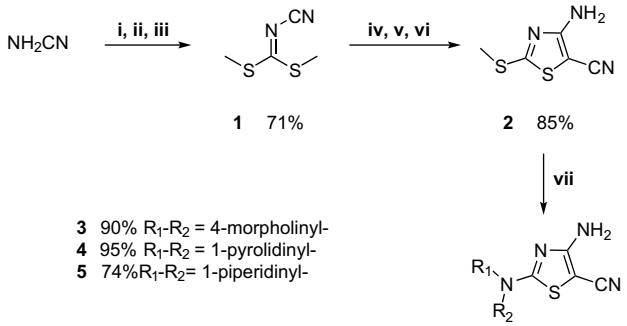
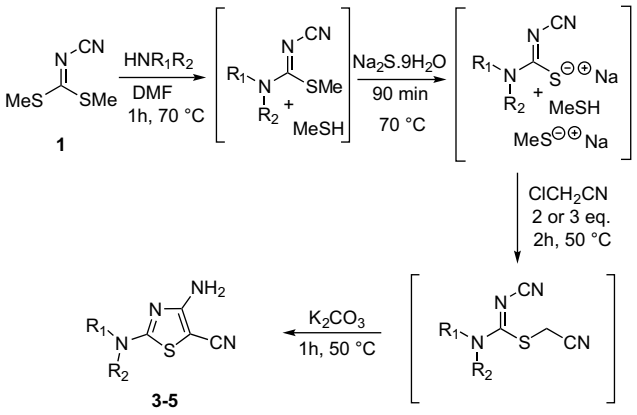
engaged in a one-pot three-step procedure and was reacted successively with sodium sulfide, chloroacetonitrile, and potassium carbonate. Finally, S_NAr on thiazole **2** with secondary amines allowed the formation of thiazoles **3**–**5** in good yields (Scheme 2).



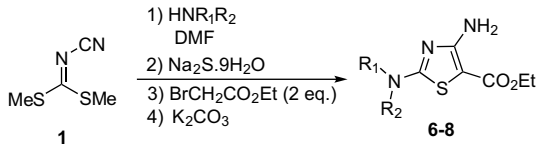
Scheme 2. Synthesis of thiazoles **3**–**5** via S_NAr reaction on thiazole **2** (Method A). Reagents and conditions: (i) KOH; (ii) CS_2; (iii) MeI; (iv) $Na_2S{\cdot}9H_2O$, DMF; (v) $ClCH_2CN$; (vi) K_2CO_3; (vii) R_1R_2NH.

In the same work, we have also used a one-pot four-step procedure to synthesize thiazoles **3**–**5** starting from **1**. Dimethyl cyanodithioimidocarbonate was dissolved in DMF, then the secondary amine was added and heated at 70 °C for 1 h. After this time, sodium sulfide was added to form the thiolate that reacted with chloroacetonitrile and finally, potassium carbonate was added to complete the cyclization (Scheme 3).

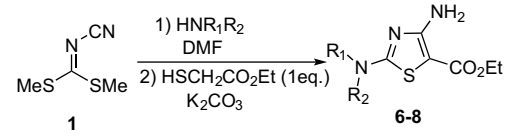


Scheme 3. Method B: one-pot four-step sequential procedure.

Method B



Method C



Scheme 4. Synthesis of ethyl 4-amino-1,3-thiazole-5-carboxylates.

Here, we completed our study on this one-pot four-step procedure in order to optimize it and extend it to other activated halides. Indeed, we performed this reaction with 1, 2 or 3 equiv of chloroacetonitrile (Table 1). When 1 equiv of chloroacetonitrile was added, no reaction was observed by TLC with the sodium salt of cyanoimidothiocarbamate. So we repeated the reaction adding 2 equiv of chloroacetonitrile and expected products **3**–**5** were obtained in good yields (49–67%, Table 1). Using 3 equiv of chloroacetonitrile, the yields were improved (69–78%, Table 1).

Table 2
Synthesis of ethyl 4-amino-1,3-thiazole-5-carboxylates

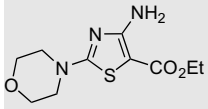
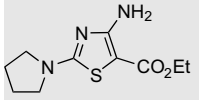
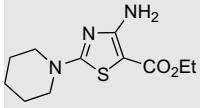
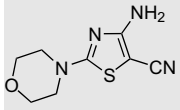
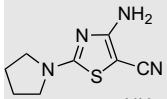
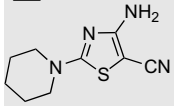
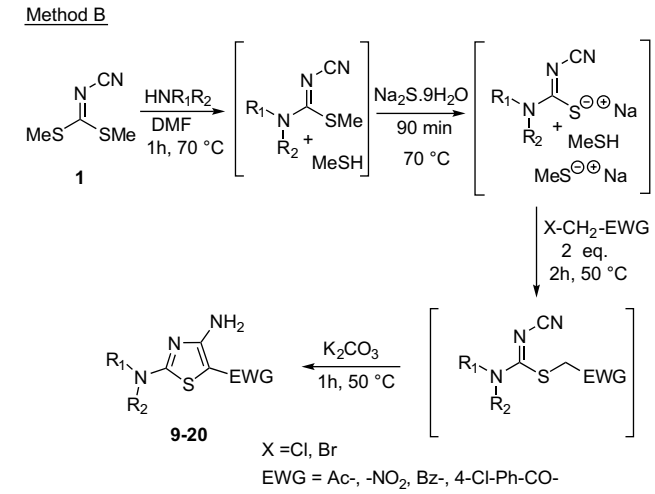
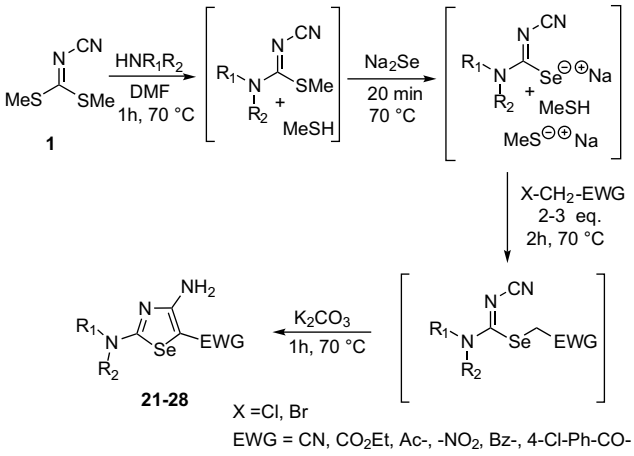
Compound	Compound no.	Yield (%)	
		Method B	Method C
	**6**	77	50
	**7**	71	65
	**8**	74	49

Table 1
Synthesis of substituted 4-amino-5-cyano-1,3-thiazoles, comparison of Methods A and B

Compound	Compound no.	Method A		Method B	
		Yield S_NAr (%)	Overall yield from **1** (%)	Yield (%) (2 equiv $ClCH_2CN$)	Yield (%) (3 equiv $ClCH_2CN$)
	**3**	90	77	57	78
	**4**	95	81	67	76
	**5**	74	63	49	69



Scheme 5. Synthesis of substituted ethyl 2,4,5-trisubstituted-1,3-thiazoles: one-pot four-step sequential procedure.



Scheme 6. Synthesis of substituted ethyl 2,4,5-trisubstituted-1,3-selenazoles: one-pot four-step sequential procedure.

These experiments showed that chloroacetonitrile reacted first with sodium methylthiolate, which is more nucleophilic than the intermediate.

We extended this method to ethyl bromoacetate. The mechanism of the reaction (Method B, Scheme 4) is similar to the previous one shown in Scheme 3. The best results were obtained adding 2 equiv of ethyl bromoacetate. The expected compounds **6**–**8** were obtained in good yields (71–77%, Table 2). An alternative to the combination of sodium sulfide/activated halide was to use ethyl thioglycolate (Method C, Scheme 4). Dimethyl cyanodithioimidocarbonate **1** was heated for 1 h with secondary amine and then ethyl thioglycolate and potassium carbonate were added and heated for 3 h. The expected compounds **6**–**8** were obtained with good yields (49–65%, Table 2). However the best yields were obtained using sodium sulfide. Moreover, we extended this reaction using other activated halides like chloroacetone, bromonitromethane,[14] chloroacetophenone, and ω-bromo-*p*-chloroacetophenone (Scheme 5).

As we presumed, the one-pot four-step sequential procedure could be applied to different activated halides and allowed the access to new 2,4,5-trisubstituted 1,3-thiazoles (Scheme 5). In all cases, the best results were obtained adding 2 equiv of reagent (Table 3). When 1 equiv of activated halide was added, no reaction was observed by TLC with the sodium salt of cyanoimidothiocarbamate. When 3 equiv were used, a mixture of the 1,3-thiazole and a viscous material was obtained after the work-up. The recrystallization was more difficult to realize and the isolated yields were lower. These experiments showed that methylthiolate is more nucleophilic than the intermediate sodium salt of cyanoimidothiocarbamate and reacts faster with all these activated halides.

In comparison with the literature, this one-pot four-step procedure presents some improvements and advantages. The yields that we obtained are very good and our method is one step shorter than the S_NAr way. Moreover, there is only one example of solid phase synthesis to access 2,4,5-trisubstituted 1,3-thiazoles in a one-pot four-step reaction.[15] Here we obtained better yields and sodium sulfide allowed the use of various activated halides and the access to 4-amino-1,3-thiazoles substituted in position 5 with interesting

Table 3
Synthesis of 2,4,5-trisubstituted-1,3-thiazoles

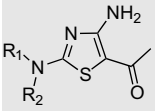
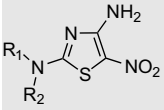
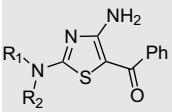
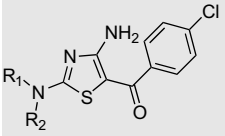
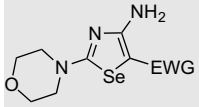
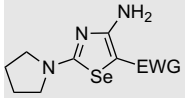
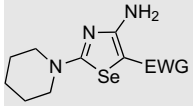
Compound	$-NR_1R_2$	Activated halide used	Compound no.	Yield (%)
	4-Morpholinyl-	Chloroacetone (2 equiv)	**9**	51
	1-Pyrolidinyl-		**10**	75
	1-Piperidinyl-		**11**	85
	4-Morpholinyl-	Bromonitromethane (2 equiv)	**12**	65
	1-Pyrolidinyl-		**13**	72
	1-Piperidinyl-		**14**	70
	4-Morpholinyl-	Chloroacetophenone (2 equiv)	**15**	76
	1-Pyrolidinyl-		**16**	82
	1-Piperidinyl-		**17**	87
	4-Morpholinyl-	ω-Bromo-*p*-chloroacetophenone (2 equiv)	**18**	48
	1-Pyrolidinyl-		**19**	65
	1-Piperidinyl-		**20**	76

Table 4
Synthesis of 2,4,5-trisubstituted-1,3-selenazoles

Compound	EWG	Halide used	Compound no.	Yield (%)
	-CN	Chloroacetonitrile (3 equiv)	**21**	55
	-Ac	Chloroacetone (2 equiv)	**22**	28
	-Ac	Chloroacetone (3 equiv)	**22**	36
	-NO_2	Bromonitromethane (2 equiv)	**23**	32
	-CN	Chloroacetonitrile (3 equiv)	**24**	70
	-CO_2Et	Ethyl bromoacetate (2 equiv)	**25**	52
	-CN	Chloroacetonitrile (3 equiv)	**26**	67
	-Bz	Chloroacetophenone (2 equiv)	**27**	41
	-4-chlorobenzoyl	ω-Bromo-*p*-chloroacetophenone (2 equiv)	**28**	50

functional groups such as cyano, ester, acetyl, nitro, and benzoyl group. We then extended this method to the preparation of 2,4,5-trisubstituted-1,3-selenazoles.

In the literature, 2-amino-1,3-selenazoles were synthesized from selenourea and α-chloroketones.[16] Ketones like cyclohexanone or deoxybenzoin were reacted in presence of selenourea and iodine and afforded 4,5-disubstituted 2-amino-1,3-selenazoles.[17] From dimethyl dicyanothioimidocarbonate **1**, we obtained in one-pot new 2,4,5-trisubtituted-1,3-selenazoles (Scheme 6).

Compound **1** was heated at 70 °C for 1 h with a secondary amine to form the first intermediate (Scheme 6). Sodium selenide was prepared freshly, filtered under argon atmosphere and was added to the reaction mixture at 70 °C to form the intermediate selenolate. After 20 min, activated halide (2–3 equiv) was added dropwise and stirred for 2 h more. Cyclization was performed by addition of potassium carbonate. Pouring the reaction mixture in water gave the compounds **21**–**28** as solids in moderate to good yields (Table 4). As for the preparation of 1,3-thiazoles **3**–**20**, we had to use at least 2 equiv of activated halide to isolate 2,4,5-trisubtituted-1,3-selenazoles **21**–**28**.

3. Conclusion

Here we demonstrated that our sequential procedure is very convenient for the synthesis of 2,4,5-trisubstituted-1,3-thiazoles and 1,3-selenazoles. We determined the conditions to obtain expected compounds in good yields. This method is shorter than the S_NAr pathway. Another advantage is that dimethyl dicyanothioimidocarbonate **1** was obtained easily and in good yield from cyanamide and was the same starting material for the preparation of all thiazoles and selenazoles. If we use this reaction on ketene dithioacetals, we will have access to tetra-substituted thiophenes and selenophenes, this work will be reported in due course.

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, 6890N 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.

Syntheses of compounds **1**–**5** are described in Ref. 8.

4.2. Synthesis of 2,4,5-trisubstituted-1,3-thiazoles

4.2.1. General method

Method B: Dimethyl cyanodithioimidocarbonate **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 1 h. Then, $Na_2S\cdot 9H_2O$ (0.01 mol) was added and heated for 90 min at 70 °C. Activated halide (0.02–0.03 mol) was added dropwise at 50 °C (0 °C for bromonitromethane). The mixture was heated at 50 °C for 2 h and potassium carbonate was added (0.01 mol). The reaction was stirred at 50 °C for 1 h 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.

Method C: Dimethyl cyanodithioimidocarbonate **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 1 h. Then ethyl thioglycolate (0.01 mol) and potassium carbonate (0.01 mol) were added and heated for 3 h at 70 °C. The mixture was poured onto water (100 mL) with good stirring. The precipitated was filtered, washed with water and dried at room temperature until constant weight, and purified by recrystallization in ethanol.

4.2.2. Ethyl 4-amino-2-(4-morpholinyl)-1,3-thiazole-5-carboxylate (*6*)

Yield: 77% (Method B); 50% (Method C). Colorless solid; mp 132 °C. IR: 3419, 3309, 3205, 1658, 1626, 1514 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.18 (t, 3H, CH_3, J=7.1 Hz), 3.43 (m, 4H, 2×CH_2), 3.66 (m, 4H, 2×CH_2), 4.08 (q, 2H, CH_2, J=7.1 Hz), 6.80 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 14.58, 47.20, 58.70, 65.22, 163.14, 163.29, 169.42, 170.46. GC–MS (EI, 70 eV): *m*/*z* (%): 257 (100), 229 (14), 212 (20), 185 (30), 113 (26), 69 (12). HRMS calcd for $C_{10}H_{16}N_3O_3S$ $[M+H]^+$ 258.0907, found 258.0909.

4.2.3. Ethyl 4-amino-2-(1-pyrrolidinyl)-1,3-thiazole-5-carboxylate (*7*)

Yield: 71% (Method B); 65% (Method C). Colorless solid; mp 200 °C. IR: 3415, 3278, 3168, 3112, 1642, 1614, 1559 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.17 (t, 3H, CH_3, J=7.1 Hz), 1.96 (m, 4H,

2×CH_2), 3.34 (m, 4H, 2×CH_2), 4.08 (q, 2H, CH_2, J=7.1 Hz), 6.81 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 14.61, 25.01, 48.88, 58.51, 79.03, 121.43, 163.65, 166.73. GC–MS (EI, 70 eV): m/z (%): 241 (100), 213 (20), 196 (23), 185 (11), 169 (37), 97 (38), 72 (10), 23 (23). HRMS calcd for $C_{10}H_{16}N_3O_2S$ $[M+H]^+$ 242.0958, found 242.0966.

*4.2.4. Ethyl 4-amino-2-(1-piperidinyl)-1,3-thiazole-5-carboxylate (**8**)*

Yield: 74% (Method B); 49% (Method C). Colorless solid; mp 145 °C. IR: 3418, 3299, 3195, 1638, 1612 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.19 (t, 3H, CH_3, J=7.1 Hz), 1.56 (m, 6H, 3×CH_2), 3.43 (br s, 4H, 2×CH_2), 4.05 (q, 2H, CH_2, J=7.1 Hz), 6.75 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 14.61, 23.34, 24.68, 48.24, 58.54, 79.23, 163.34, 163.73, 169.86. GC–MS (EI, 70 eV): m/z (%): 255 (100), 183 (37), 111 (30). HRMS calcd for $C_{11}H_{18}N_3O_2S$ $[M+H]^+$ 256.1114, found 256.1093.

*4.2.5. 5-Acetyl-4-amino-2-(4-morpholinyl)-1,3-thiazole (**9**)*

Yield: 51% (Method B). Yellow solid; mp: 174 °C. IR: 3370, 3262, 3160, 1606 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.05 (s, 3H, CH_3), 3.46 (m, 4H, 2×CH_2), 3.67 (m, 4H, 2×CH_2), 7.60 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 28.66, 47.35, 65.24, 93.70, 163.68, 170.24, 184.58. GC–MS (EI, 70 eV): m/z (%): 227 (100), 212 (67), 184 (13), 154 (16), 113 (24), 69 (12). HRMS calcd for $C_9H_{14}N_3O_2S$ $[M+H]^+$ 228.0801, found 228.0787.

*4.2.6. 5-Acetyl-4-amino-2-(1-pyrrolidinyl)-1,3-thiazole (**10**)*

Yield: 75% (Method B). Yellow solid; mp 181 °C. IR: 3315, 3171, 1643, 1528 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.93 (m, 4H, 2×CH_2), 1.98 (s, 3H, CH_3), 3.38 (m, 4H, 2×CH_2), 7.65 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.99, 28.68, 49.04, 93.73, 164.22, 166.59, 183.93. GC–MS (EI, 70 eV): m/z (%): 211 (100), 196 (87), 168 (23), 97 (36), 55 (23). HRMS calcd for $C_9H_{14}N_3OS$ $[M+H]^+$ 212.0852, found 212.0861.

*4.2.7. 5-Acetyl-4-amino-2-(1-piperidinyl)-1,3-thiazole (**11**)*

Yield: 85% (Method B). Yellow solid; mp 173 °C. IR: 3327, 3238, 3129, 1611, 1544 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.58 (m, 6H, 3×CH_2), 2.02 (s, 3H, CH_3), 3.47 (m, 4H, 2×CH_2), 7.60 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 23.34, 24.75, 28.64, 48.46, 93.49, 164.10, 169.59, 184.10. GC–MS (EI, 70 eV): m/z (%): 225 (100), 210 (76), 196 (3). HRMS calcd for $C_{10}H_{16}N_3OS$ $[M+H]^+$ 226.1009, found 226.1011.

*4.2.8. 4-Amino-2-(4-morpholinyl)-5-nitro-1,3-thiazole (**12**)*

Yield: 65% (Method B). Brown solid; mp 219 °C. IR: 3348, 3257, 3137, 1607, 1552 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 3.56 (br s, 4H, 2×CH_2), 3.68 (br s, 4H, 2×CH_2), 8.20 (br s, 1H, NH_2), 8.93 (br s, 1H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 44.00, 65.15, 109.72, 160.16, 168.04. GC–MS (EI, 70 eV): m/z (%): 230 (100), 184 (38), 113 (69), 69 (33). HRMS calcd for $C_7H_{10}N_4O_3SNa$ $[M+Na]^+$ 253.0366, found 253.0342.

*4.2.9. 4-Amino-5-nitro-2-(1-pyrrolidinyl)-1,3-thiazole (**13**)*

Yield: 72% (Method B). Brown solid; mp 247 °C. IR: 3401, 3104, 1620, 1571 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.96 (m, 4H, 2×CH_2), 3.37 (m, 2H, CH_2), 3.58 (m, 2H, CH_2), 8.15 (br s, 1H, NH_2), 8.94 (br s, 1H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.78, 49.18, 109.87, 160.36, 164.77. GC–MS (EI, 70 eV): m/z (%): 214 (100), 140 (40), 97 (92), 72 (27), 55 (48). HRMS calcd for $C_7H_{11}N_4O_2S$ $[M+H]^+$ 215.0597, found 215.0601.

*4.2.10. 4-Amino-5-nitro-2-(1-piperidinyl)-1,3-thiazole (**14**)*

Yield: 70% (Method B). Brown solid; mp 220 °C. IR: 3413, 3284, 1624, 1566 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.59 (m, 6H, 3×CH_2), 3.54 (m, 4H, 2×CH_2), 8.17 (br s, 1H, NH_2), 8.86 (br s, 1H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 21.32, 22.84, 24.87, 109.65, 160.56, 167.20. GC–MS (EI, 70 eV): m/z (%): 194 (100), 165 (55), 139 (26), 83 (39), 69 (19), 55 (37). HRMS calcd for $C_8H_{13}N_4O_2S$ $[M+H]^+$ 229.0754, found 229.0735.

*4.2.11. 4-Amino-5-benzoyl-2-(4-morpholinyl)-1,3-thiazole (**15**)*

Yield: 76% (Method B). Colorless solid; mp 181 °C; lit. mp: 179–181 °C.[2b] IR: 3370, 3230, 3134, 1599, 1534 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 3.48 (m, 4H, 2×CH_2), 3.66 (m, 4H, 2×CH_2), 7.45 (m, 3H, 3×CH), 7.61 (m, 2H, 2×CH), 8.07 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 47.43, 65.25, 92.95, 126.60, 128.30, 130.71, 141.87, 166.06, 171.79, 182.15. GC–MS (EI, 70 eV): m/z (%): 289 (100), 230 (15), 203 (15), 105 (20), 77 (24). HRMS calcd for $C_{14}H_{16}N_3O_2S$ $[M+H]^+$ 290.0958, found 290.0955.

*4.2.12. 4-Amino-5-benzoyl-2-(1-pyrrolidinyl)-1,3-thiazole (**16**)*

Yield: 82% (Method B). Yellow solid; mp 181 °C. IR: 3289, 3135, 1604, 1537 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.94 (m, 4H, 2×CH_2), 3.45 (m, 4H, 2×CH_2), 7.45 (m, 3H, 3×CH), 7.61 (m, 2H, 2×CH), 8.25 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.96, 49.08, 93.11, 126.58, 128.66, 130.00, 142.01, 166.54, 168.18, 181.53. GC–MS (EI, 70 eV): m/z (%): 273 (100), 196 (14), 97 (20), 77 (24). HRMS calcd for $C_{14}H_{16}N_3OS$ $[M+H]^+$ 274.1009, found 274.1069.

*4.2.13. 4-Amino-5-benzoyl-2-(1-piperidinyl)-1,3-thiazole (**17**)*

Yield: 87% (Method B). Yellow solid; mp 160 °C; lit. mp: 159–160 °C.[2b] IR: 3354, 3225, 3138, 1599, 1529 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.60 (m, 6H, 3×CH_2), 3.48 (m, 4H, 2×CH_2), 7.44 (m, 3H, 3×CH), 7.61 (m, 2H, 2×CH), 8.25 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 23.31, 24.80, 48.54, 92.81, 126.92, 128.42, 130.02, 142.02, 166.52, 171.11, 181.71. GC–MS (EI, 70 eV): m/z (%): 287 (100), 105 (18), 77 (21). HRMS calcd for $C_{15}H_{18}N_3OS$ $[M+H]^+$ 288.1165, found 288.1166.

*4.2.14. 4-Amino-5-(4-chlorobenzoyl)-2-(4-morpholinyl)-1,3-thiazole (**18**)*

Yield: 48% (Method B). Yellow solid; mp 135 °C; lit. mp: 151–152 °C.[2b] IR: 3366, 3272, 1614, 1535 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 3.45 (m, 4H, 2×CH_2), 4.37 (m, 4H, 2×CH_2), 7.52 (m, 2H, 2×CH), 7.62 (m, 2H, 2×CH), 8.15 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 47.48, 65.24, 92.85, 128.40, 128.56, 134.79, 140.50, 166.34, 171.76, 180.53. GC–MS (EI, 70 eV): m/z (%): 323 (100), 264 (15), 139 (25), 113 (23), 69 (13). HRMS calcd for $C_{14}H_{15}ClN_3O_2S$ $[M+H]^+$ 324.0568, found 324.0585.

*4.2.15. 4-Amino-5-(4-chlorobenzoyl)-2-(1-pyrrolidinyl)-1,3-thiazole (**19**)*

Yield: 65% (Method B). Yellow solid; mp 210 °C. IR: 3271, 3145, 1594, 1542 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.95 (m, 4H, 2×CH_2), 3.50 (m, 4H, 2×CH_2), 7.52 (m, 2H, 2×CH), 7.65 (m, 2H, 2×CH), 8.25 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.97, 49.16, 93.00, 128.36, 130.34, 133.97, 140.71, 166.79, 168.16, 179.90. GC–MS (EI, 70 eV): m/z (%): 307 (100), 196 (14), 139 (22), 111 (22), 97 (27), 55 (25). HRMS calcd for $C_{14}H_{14}ClN_3OS$ $[M+H]^+$ 308.0619, found 308.0603.

*4.2.16. 4-Amino-5-(4-chlorobenzoyl)-2-(1-piperidinyl)-1,3-thiazole (**20**)*

Yield: 76% (Method B). Yellow solid; mp 175 °C. IR: 3336, 3253, 1592, 1538 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.57 (m, 6H, 3×CH_2), 3.48 (m, 4H, 2×CH_2), 7.50 (d, 2H, 2×CH, J=8.4 Hz), 7.65 (d, 2H, 2×CH, J=8.4 Hz), 8.25 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 23.29, 24.81, 48.60, 92.72, 128.34, 128.64, 133.97, 139.62, 166.79, 171.06, 180.06. GC–MS (EI, 70 eV): m/z (%): 321 (100), 139 (25), 111 (40). HRMS calcd for $C_{15}H_{17}ClN_3OS$ $[M+H]^+$ 322.0775, found 322.0791.

4.3. Preparation of sodium selenide

Selenium (0.01 mol) was added to a solution of NaOH (0.056 mol) and sodium formaldehyde sulfoxylate (0.024 mol) in water (10 mL). After stirring for 1 h at 50 °C, the white precipitate was filtered under argon atmosphere and rapidly used for the next step.

4.4. Synthesis of substituted 4-amino-1,3-selenazoles

Dimethyl cyanodithioimidocarbonate **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 1 h. 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 (0 °C for bromonitromethane). 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. When a precipitate appeared, it was filtered, washed with water, and dried at room temperature until constant weight. When a viscous mixture appeared, the solution was extracted with ether (3×25 mL). The organic layers were dried with $MgSO_4$, filtered, and evaporated. The isolated solid was purified by recrystallization in acetonitrile.

*4.4.1. 4-Amino-2-(4-morpholinyl)-1,3-selenazole-5-carbonitrile (**21**)*

Yield: 55%. Brown solid; mp 209 °C. IR: 3344, 2178, 1658 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 3.39 (m, 4H, 2×CH_2), 3.63 (m, 4H, 2×CH_2), 6.72 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 47.36, 56.16, 65.26, 118.30, 166.21, 171.31. GC–MS (EI, 70 eV): *m*/*z* (%): 258 (100), 243 (0.5). HRMS calcd for $C_8H_{11}N_4OSe$ $[M+H]^+$ 259.0093, found 259.0085.

*4.4.2. 5-Acetyl-4-amino-2-(4-morpholinyl)-1,3-selenazole (**22**)*

Yield: 28% (2 equiv of $ClCH_2COCH_3$); 36% (3 equiv of $ClCH_2COCH_3$). Brown solid; mp 164 °C. IR: 3252, 1588, 1526 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 2.04 (s, 3H, CH_3), 3.46 (m, 4H, 2×CH_2), 3.67 (m, 4H, 2×CH_2), 7.62 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 28.65, 47.35, 65.24, 93.71, 163.68, 170.23, 184.57. GC–MS (EI, 70 eV): *m*/*z* (%): 275 (100), 260 (64), 246 (0.9). HRMS calcd for $C_9H_{14}N_3OSe$ $[M+H]^+$ 276.0246, found 276.0220.

*4.4.3. 4-Amino-2-(4-morpholinyl)-5-nitro-1,3-selenazole (**23**)*

Yield: 32%. Orange solid; mp 249 °C. IR: 3268, 2360, 1619, 1394, 1274 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 3.33 (m, 4H, 2×CH_2), 3.67 (m, 4H, 2×CH_2), 8.45 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 65.15, 65.27, 109.99, 162.12, 168.73. GC–MS (EI, 70 eV): *m*/*z* (%): 278 (93). HRMS calcd for $C_7H_{10}N_4O_3SeNa$ $[M+Na]^+$ 300.9810, found 300.9802.

*4.4.4. 4-Amino-2-(1-pyrrolidinyl)-1,3-selenazole-5-carbonitrile (**24**)*

Yield: 70%. Brown solid; mp 302 °C. IR: 3169, 2165, 1646 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.94 (m, 4H, 2×CH_2), 3.36 (m, 4H, 2×CH_2), 6.60 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 25.02, 49.11, 118.66, 165.47, 166.51, 166.97. GC–MS (EI, 70 eV): *m*/*z* (%): 242 (100), 227 (0.5). HRMS calcd for $C_8H_{11}N_4Se$ $[M+H]^+$ 243.0143, found 243.0144.

*4.4.5. Ethyl 4-amino-2-(1-pyrrolidinyl)-1,3-selenazole-5-carboxylate (**25**)*

Yield: 52%. Brown solid; mp 199 °C. IR: 3171, 1727, 1641 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.16 (t, *J*=7.5 Hz, 3H, CH_3), 1.94 (m, 4H, 2×CH_2), 3.41 (m, 4H, 2×CH_2), 4.06 (q, *J*=7.5 Hz, 2H, CH_2), 6.80 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 14.61, 25.01, 48.87, 58.51, 163.40, 166.72, 167.07, 170.02. GC–MS (EI, 70 eV): *m*/*z* (%): 289 (100), 274 (0.5), 261 (12). HRMS calcd for $C_{10}H_{16}N_3O_2Se$ $[M+H]^+$ 290.0402, found 290.0400.

*4.4.6. 4-Amino-2-(1-piperidinyl)-1,3-selenazole-5-carbonitrile (**26**)*

Yield: 67%. Pale brown solid; mp 236 °C. IR: 3362, 3201, 2170, 1641 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.54 (m, 6H, 3×CH_2), 3.35 (m, 4H, 2×CH_2), 6.63 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 23.32, 24.83, 48.52, 56.29, 116.77, 166.53, 170.29. GC–MS (EI, 70 eV): *m*/*z* (%): 256 (100), 241 (4). HRMS calcd for $C_9H_{13}N_4Se$ $[M+H]^+$ 257.0300, found 257.0301.

*4.4.7. 4-Amino-5-benzoyl-2-(1-piperidinyl)-1,3-selenazole (**27**)*

Yield: 41%. Green solid; mp 166 °C. IR: 3637, 1598, 1527 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.57 (m, 6H, 3×CH_2), 3.48 (m, 4H, 2×CH_2), 7.43 (m, 3H, 3×CH), 7.60 (m, 2H, 2×CH), 8.50 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 23.21, 24.80, 48.54, 92.79, 126.60, 128.28, 130.03, 142.01, 166.51, 172.00, 181.71. GC–MS (EI, 70 eV): *m*/*z* (%): 335 (100). HRMS calcd for $C_{15}H_{18}N_3OSe$ $[M+H]^+$ 336.0610, found 336.0619.

*4.4.8. 4-Amino-5-(4-chlorobenzoyl)-2-(1-piperidinyl)-1,3-selenazole (**28**)*

Yield: 50%. Green solid; mp 167 °C. IR: 3337, 1670, 1539 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.57 (m, 6H, 3×CH_2), 3.49 (m, 4H, 2×CH_2), 7.48 (m, 2H, 2×CH), 7.59 (m, 2H, 2×CH), 8.45 (br s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 23.39, 24.82, 48.67, 93.22, 128.09, 128.36, 134.39, 140.63, 168.08, 171.89, 181.82. GC–MS (EI, 70 eV): *m*/*z* (%): 369 (100). HRMS calcd for $C_{15}H_{17}ClN_3OSe$ $[M+H]^+$ 370.0220, found 370.0235.

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