An efficient one-pot synthesis of 2-amino-1,3,4-selenadiazoles

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An efficient one-pot synthesis of 2-amino-1,3,4-selenadiazoles from isoselenocyanates, hydrazine hydrate and aromatic aldehydes has been developed. This approach provides a simple, mild and facile way to construct various derivatives in moderate to good yields (57–82%). A plausible mechanism is proposed for the formation of the target products.

Keywords: isoselenocyanates, selenosemicarbazides, selenohydrazones, selenoheterocycle, selenadiazoles

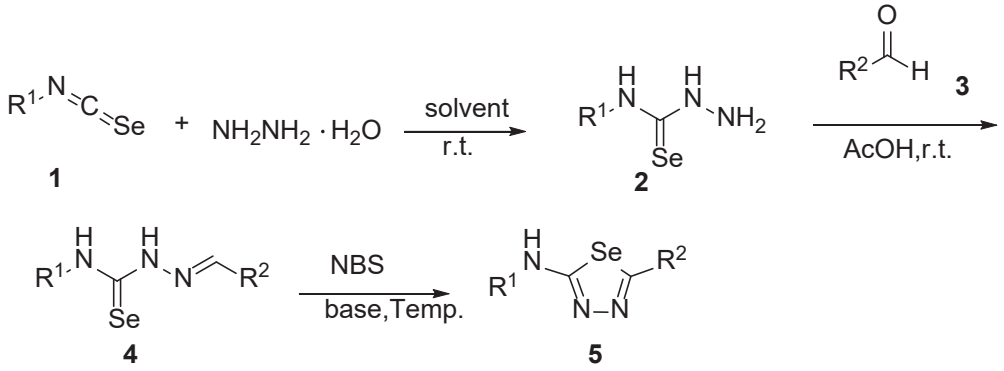
Selenium-containing heterocycles have been recognised to play an important role in both synthetic chemistry[1,2] and medicinal biology as biological response modifiers.[3–6] As five-membered selenium-containing heterocycles, 1,3,4-selenadiazoles have been studied for decades due to their potential anti-bacterial, anti-tumour, anti-convulsant and anti-inflammatory activities.[7,8] Besides, some 1,3,4-selenadiazoles have been reported as thermotropic liquid crystals and metal ion complexation reagents.[9–12] As a result, a variety of approaches have been developed to synthesise 1,3,4-selenadiazoles. Stolle[13] obtained 1,3,4-selenadiazoles from reacting 1,2-diacetylhydrazine with phosphorus pentaselenide. Kendall[14] reported the reaction of dimethylformamide azine with hydrogen selenide to form 1,3,4-selenadiazoles. In 1973, Bulka[15,16] *et al.* prepared 2-(arylamino)-5-aryl-1,3,4-selenadiazoles or 2,5-diamino-1,3,4-selenadiazoles from the cyclodehydration of RNH(C=Se)NHNHCOR′ or RNH(C=Se)NHNH(C=Se)NHR′ (R, R′ = H, Me, Ar) in concentrated H_2SO_4 or Ac_2O. Cohen[17] described a method for the synthesis of 1,3,4-selenadiazoles from selenobenzamides with hydrazine hydrate. In 2009, Hua *et al.*[18] used 2,4-diphenyl-1,3-diselenadiphosphetane-2,4-diselenide (Woollins' reagent) as selenation reagent to react with 1,2-diacylhydrazines to prepare 1,3,4-selenadiazoles. However, all the procedures to date have severe environmental or safety concerns as they involve toxic reagents such as hydrogen selenide, high reaction temperatures and tedious manipulative procedures.

Isoselenocyanates were widely employed in the synthesis of selenium-containing heterocycles due to their convenient preparation, low toxicity, relative stability and excellent reactivity.[19–23] We have been interested in the synthesis of 1,3,4-selenadiazoles. Very recently, we developed an efficient one-pot synthesis of 2-amino-1,3,4-selenadiazoles from isoselenocyanates, hydrazine hydrate and aromatic aldehydes (Scheme 1). This approach provides a simple, mild and facile way to construct various 2-amino-1,3,4-selenadiazoles in moderate to good yields (57–82%).

Result and discussion

Initially, phenyl selenohydrazone (**4a**) was selected to optimise the ring-closure reaction conditions. The effects of solvent, reaction temperature, the amount of *N*-bromosuccinimide (NBS) and different bases were investigated. The results are shown in Table 1. Among all the solvents CH_2Cl_2 proved to be the optimal one since a 71% yield could be obtained (Table 1, entries 1–5). Unfortunately, deselenisation was observed when THF or CH_3CN was used as the solvent. The reaction proceeded more efficiently at 40 °C (reflux) than at 35 °C (Table 1, entries 5 and 6). Prolonged reaction times at 40 °C did not greatly enhance the yield (Table 1, entry 7). The reaction failed completely in the absence of base (Table 1, entry 8). Various bases, such as NaOAc, $NaHCO_3$, Na_2CO_3 and triethylamine (TEA) were investigated and NaOAc was found to be the most promising (Table 1, entries 5, 9–11). To further improve the yield, the effect of altering the amount of NBS was investigated (Table 1, entries 5, 13 and 14). The yield was improved to 85% by increasing the amount of NBS to 1.5 equiv. Furthermore, there was no product in the absence of NBS (Table 1, entry 12). So, the optimal reaction conditions were established as using 1.5 equiv. of NBS, NaOAc as base and CH_2Cl_2 as solvent under reflux.

With the optimised conditions in hand, we set out to explore the substrate scope. Selenosemicarbazides **2** could be prepared conveniently from isoselenocyanates **1a**–**e**[24,25] and hydrazine



Scheme 1 Preparation of 2-amino-1,3,4-selenadiazoles from isoselenocyanates, hydrazine hydrate and aldehydes.

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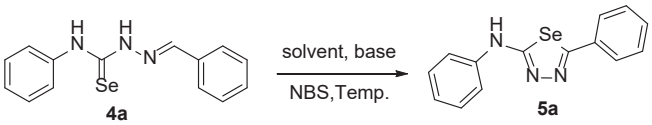
Table 1 Optimisation of reaction conditions for the synthesis of 2-amino-1,3,4-selenadiazoles *via* cycloselenisation



4a **5a**

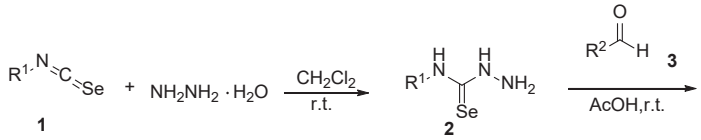
Entry	Solvent	Base (2.0 equiv.)	NBS (equiv.)	Temp. /°C	Time[a] /h	Yield[b] /%
1	CH_3CN	NaOAc	1.4	40	12	< 10
2	EtOAc	NaOAc	1.4	40	12	20
3	$ClCH_2CH_2Cl$	NaOAc	1.4	40	12	60
4	THF	NaOAc	1.4	40	12	trace
5	CH_2Cl_2	NaOAc	1.4	reflux	2	71
6	CH_2Cl_2	NaOAc	1.4	35	12	75
7	CH_2Cl_2	NaOAc	1.4	reflux	12	80
8	CH_2Cl_2	none	1.4	reflux	12	none
9	CH_2Cl_2	Na_2CO_3	1.4	reflux	2	trace
10	CH_2Cl_2	$NaHCO_3$	1.4	reflux	2	trace
11	CH_2Cl_2	TEA	1.4	reflux	2	< 10
12	CH_2Cl_2	NaOAc	none	reflux	12	none
13	CH_2Cl_2	NaOAc	1.5	reflux	2	85
14	CH_2Cl_2	NaOAc	1.6	reflux	2	85

[a]Monitored by TLC.

[b]Isolated yield based on **4a**.

hydrate, then further reacted with aldehyde **3** to form the corresponding selenohydrazones **4** under AcOH catalysis in CH_2Cl_2 at room temperature. Subsequently, 2-amino-1,3,4-selenadiazoles **5** could be observed after NaOAc and NBS were directly added to the above mixture in one pot and then heated to reflux. The results are summarised in Table 2. Various 2-amino-1,3,4-selenadiazoles were prepared in moderate to good yields (57–82%). The nature of the R^2 group on the aldehydes **3** affected the reaction yields to some degree (Table 2, entries 1–4). Aldehydes substituted with electron-donating groups [Table 2, entries 3 (78%) and 4 (77%)] provided slightly higher yields than those having an electron-withdrawing group [Table 2, entry 2 (71%)]. The substituents on the isoselenocyanates also affected the reaction yields. Thus, isoselenocyanates with electron-donating substituents (Table 2, entries 6 and 7) afforded higher yields than those with an electron-withdrawing substituent (Table 2, entry 5). Therefore, 2-amino-1,3,4-selenadiazoles **5** could be obtained with the best yields (79–82%) when R^1 and R^2 were both electron-donating groups (Table 2, entries 10–14). However, when aldehyde **3f** reacted with isoselenocyanate (**1c**) (Table 2, entry 8), the yield decreased due to the steric effect, compared with aldehydes **3b** (Table 2, entry 9). Cyclohexyl isoselenocyanate (**1e**) also provided the desired product in 60% yield (Table 2, entry 16).

Table 2 One-pot synthesis of 2-amino-1,3,4-selenadiazoles **5** from isoselenocyanates, hydrazine hydrate and aldehydes **3**

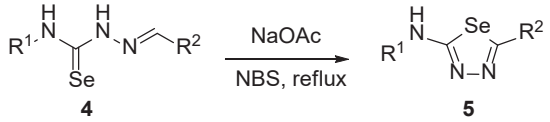


1

1a: R^1= C_6H_5; **1b**: R^1= 4-ClC_6H_4;
1c: R^1= 4-$CH_3C_6H_4$; **1d**: R^1= 4-$CH_3OC_6H_4$;
1e: R^1= Cyclohexyl;

2

3a: R^2 = C_6H_5; **3b**: R^2= 4-ClC_6H_4;
3c: R^2= 4-$CH_3C_6H_4$; **3d**: R^2= 4-$CH_3OC_6H_4$;
3e: R^2= 3-$CH_3OC_6H_4$; **3f**: R^2= 2-ClC_6H_4;



4 **5**

Entry	R^1	R^2	Products[a]	Yield[b]/%
1	C_6H_5	C_6H_5	**5a**	73
2	C_6H_5	4-ClC_6H_4	**5b**	71
3	C_6H_5	4-$CH_3C_6H_4$	**5c**	78
4	C_6H_5	3-$CH_3OC_6H_4$	**5d**	77
5	4-ClC_6H_4	C_6H_5	**5e**	57
6	4-CH_3C_6H4	$C_{6H}5$	**5f**	77
7	4-$CH_3OC_6H_4$	C_6H_5	**5g**	79
8	4-$CH_3C_6H_4$	2-ClC_6H_4	**5h**	64
9	4-$CH_3C_6H_4$	4-ClC_6H_4	**5i**	71
10	4-$CH_3C_6H_4$	3-$CH_3OC_6H_4$	**5j**	79
11	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	**5k**	80
12	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	**5l**	78
13	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	**5m**	81
14	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	**5n**	82
15	4-$CH_3OC_6H_4$	4-ClC_6H_4	**5o**	74
16	Cyclohexyl	C_6H_5	**5p**	60

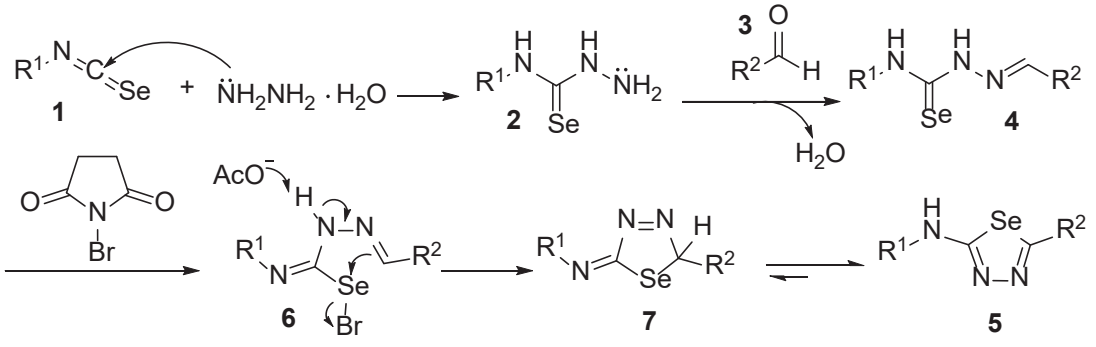
[a]Confirmed by IR, ^1H and ^{13}C NMR, MS-ESI, HRMS-ESI.

[b]Isolated yield based on **1**.

A plausible mechanism is proposed for the formation of 2-amino-1,3,4-selenadiazoles **5** in Scheme 2. Firstly, selenosemicarbazides **2,** generated rapidly and efficiently from isoselenocyanates **1** and hydrazine hydrate, reacted with aldehydes **3** to form the selenohydrazones **4**. Subsequently, selenohydrazones **4** were attacked by NBS and converted to the intermediate selenenyl bromide (**6**). Then the iminoselenadiazoles **7** were obtained *via* intramolecular cyclisation of **6** using NaOAc as base and could then aromatise (following a prototropic shift) directly to the products **5**.

Conclusion

In conclusion, a facile and efficient one-pot synthesis of 2-amino-1,3,4-selenadiazoles **5** has been developed starting



Scheme 2 Plausible mechanism proposed for the formation of **5.**

from isoselenocyanates **1**, hydrazine hydrate and aromatic aldehydes **3** in moderate to good yields. The procedure obviates the need to isolate the two intermediates **2** and **4**. This method possesses the advantages of short reaction times, mild reaction conditions and good tolerance of functional groups, making it an attractive procedure for the for the synthesis of 2-amino-1,3,4-selenadiazoles **5**.

Experimental

Infrared Spectra were determined on a Nicolet Avatar-370 spectrophotometer in KBr. Melting points were measured on a Büchi B-540 capillary melting point apparatus and are uncorrected. Mass spectra (ESI-MS) were determined on a Thermo Finnigan LCQ-Advantage instrument. High resolution mass spectra (ESI-HRMS) were determined on an Agilent 6210 TOF instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus-400 spectrometer (400 and 100 MHz) using TMS as internal standard.

Synthesis of 2-amino-1,3,4-selenadiazoles **5a**–**p** *(***5a** *was selected as an example); general procedure*

A mixture of phenyl isoselenocyanate (**1a**) (0.182 g, 1.0 mmol) and hydrazine hydrate (0.063 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was stirred for about 0.5 h at room temperature until total consumption of the starting material, monitored by TLC. Benzaldehyde (**3a**) (0.106 g, 1.0 mmol) and HOAc (0.066 g, 1.1 mmol) were added and the resulting mixture was stirred at room temperature for 1 h to prepare phenyl selenohydrazone (**4a**). Then NBS (0.267 g, 1.5 mmol) and NaOAc (0.164 g, 2.0 mmol) were added directly to this mixture and the whole was stirred at reflux for 2 h. After the reaction was complete, the reaction mixture was filtered. The filtrate was washed with brine (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography using petroleum ether–EtOAc (6:1) (60–90 °C) as eluent to afford 5-phenyl-2-phenylamino-1,3,4-selenadiazole (**5a**) as: Pink crystals, yield 0.230 g (73%); m.p. 207.0–207.5 °C (lit.[15] 208–209 °C); IR (KBr) (ν_{max} cm^{-1}): 3446, 1614, 1565, 1495, 1450, 1246, 1107, 746; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.54 (s, 1H, NH), 7.83–7.80 (m, 2H, ArH), 7.66 (d, *J* = 8.0 Hz, 2H, ArH), 7.48–7.46 (m, 3H, ArH), 7.35 (t, *J* = 8.0 Hz, 2H, ArH), 7.02 (t, *J* = 7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 162.9, 140.6, 133.0, 129.8, 128.94, 128.88, 127.3, 122.0, 117.4; ESI-MS *m/z* (%): 300 (51), 302 ([M + H]$^+$,100); HRMS-ESI calcd for $C_{14}H_{12}N_3{}^{80}Se$: (M + H)$^+$: 302.0191; found: 302.0193.

5-(4-Chlorophenyl)-2-(phenylamino)-1,3,4-selenadiazole (**5b**): Yellow crystals; yield 71%; m.p. 209.6–212.0 °C (lit.[15] 213–214 °C); IR (KBr) (ν_{max} cm^{-1}): 3442, 1620, 1601, 1502, 1451, 1418, 1089, 1013, 829, 744; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.54 (s, 1H, NH), 7.83 (d, *J* = 8.8 Hz, 2H, ArH), 7.66 (d, *J* = 7.6 Hz, 2H, ArH), 7.53 (d, *J* = 8.8 Hz, 2H, ArH), 7.35 (t, *J* = 7.6 Hz, 2H ArH), 7.03 (t, *J* = 7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.5, 140.5, 134.3, 131.9, 129.3, 129.0, 128.9, 128.8, 122.1, 117.5; ESI-MS *m/z* (%): 334 (40), 336 ([M + H]$^+$,100), 338 (45); HRMS-ESI calcd for $C_{14}H_{11}{}^{35}ClN_3{}^{80}Se$: (M + H)$^+$: 335.9799; found: 335.9800.

5-(4-Methylphenyl)-2-(phenylamino)-1,3,4-selenadiazole (**5c**): Yellow solid; yield 78%; m.p. 208.5–210.0 °C; IR (KBr) (ν_{max} cm^{-1}): 3241, 1601, 1573, 1453, 1423, 1214, 1093, 805, 744, 684; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H, NH), 7.71–7.65 (m, 4H, ArH), 7.35 (t, *J* = 7.6 Hz, 2H, ArH), 7.28 (d, *J* = 8.0 Hz, 2H, ArH), 7.02 (t, *J* = 7.2 Hz, 1H, ArH), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.6, 140.6, 139.5, 131.4, 130.3, 129.3, 128.7, 127.1, 121.8, 117.4, 20.8; MS (ESI) *m/z* (%): 314 (45), 316 ([M + H]$^+$, 100); HRMS-ESI calcd for $C_{15}H_{14}N_3{}^{80}Se$: (M + H)$^+$: 316.0348; found: 316.0336.

5-(3-Methoxyphenyl)-2-(phenylamino)-1,3,4-selenadiazole (**5d**): Yellow solid; yield 77%; m.p. 163.5–164.5 °C; IR (KBr) (ν_{max} cm^{-1}): 3450, 1599, 1571, 1506, 1421, 1273, 1181, 1077, 862, 746, 682; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45–7.38 (m, 5H, ArH), 7.34–7.26 (m, 2H, ArH), 7.15 (t, *J* = 7.2 Hz, 1H, ArH), 6.98–6.95 (m, 1H, ArH), 3.87 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.5, 161.9, 159.7, 141.2, 134.4, 129.9, 129.6, 124.0, 120.5, 118.5, 116.2, 111.9, 55.5; MS (ESI) *m/z* (%): 330 (48), 332 ([M + H]$^+$, 100); HRMS-ESI calcd for $C_{15}H_{14}N_3O^{80}Se$: (M + H)$^+$: 332.0297; found: 332.0287.

2-(4-Chlorophenylamino)-5-phenyl-1,3,4-selenadiazole (**5e**): Yellow solid; yield 57%; m.p. 218.1–220.0 °C; IR (KBr) (ν_{max} cm^{-1}): 3442, 1616, 1562, 1497, 1430, 1211, 1096, 827; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.64 (s, 1H, NH), 7.82–7.80 (m, 2H, ArH), 7.71 (d, *J* = 8.0 Hz, 2H, ArH), 7.47 –7.45 (m, 3H, ArH), 7.40 (d, *J* = 8.0 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.7, 163.6, 139.3, 132.9, 130.0, 129.0, 128.7, 127.4, 125.3, 118.9; MS (ESI) *m/z* (%): 334 (48), 336 ([M + H]$^+$, 100), 338 (45); HRMS-ESI calcd for $C_{14}H_{11}{}^{35}ClN_3{}^{80}Se$: (M + H)$^+$: 335.9799; found: 335.9783.

2-(4-Methylphenylamino)-5-phenyl-1,3,4-selenadiazole (**5f**): Yellow crystals; yield 77%; m.p. 178.8–179.5 °C; IR (KBr) (ν_{max} cm^{-1}): 3450, 1613, 1566, 1515, 1433, 1259, 1206, 1096, 824; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.42 (s, 1H, NH), 7.81–7.78 (m, 2H, ArH), 7.54 (d, *J* = 8.0 Hz, 2H, ArH), 7.48–7.45 (m, 3H, ArH), 7.15 (d, *J* = 8.0 Hz, 2H, ArH), 2.27 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 162.3, 138.2, 133.0, 130.9, 129.7, 129.2, 128.9, 127.2, 117.5, 20.4; MS (ESI) *m/z* (%): 314 (46), 316 ([M + H]$^+$, 100); HRMS-ESI calcd for $C_{15}H_{14}N_3{}^{80}Se$: (M + H)$^+$: 316.0348; found: 316.0333.

2-(4-Methoxyphenylamino)-5-phenyl-1,3,4-selenadiazole (**5g**): Yellow crystals; yield 79%; m.p. 172.8–173.5 °C; IR (KBr) (ν_{max} cm^{-1}): 3449, 1624, 1562, 1497, 1415, 1247, 1176, 965, 835; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.33 (s, 1H, NH), 7.79–7.77 (m, 2H, ArH), 7.57 (d, *J* = 8.8 Hz, 2H, ArH), 7.45–7.43 (m, 3H, ArH), 6.94 (d, *J* = 8.8 Hz, 2H, ArH), 3.74 (s, 3H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.9, 161.2, 160.1, 154.4, 134.3, 128.3, 125.7, 119.2, 114.1,114.0, 55.1; MS (ESI) *m/z* (%): 328 (48), 330 ([M – H]$^-$, 100); HRMS-ESI calcd for $C_{15}H_{14}N_3O^{80}Se$: (M + H)$^+$: 332.0297; found: 332.0286.

5-(2-Chlorophenyl)-2-(4-methylamino)-1,3,4-selenadiazole (**5h**): Yellow solid; yield 64%; m.p. 213.1–214.5 °C; IR (KBr) (ν_{max} cm^{-1}): 3443, 1610, 1564, 1424, 1292, 1108, 1032, 836, 750; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.47 (s, 1H, NH), 8.10–8.08 (m, 1H, ArH), 7.64–7.61 (m, 1H, ArH), 7.56 (d, *J* = 8.0 Hz, 2H, ArH), 7.49–7.47 (m, 2H, ArH), 7.16 (d, *J* = 8.0 Hz, 2H, ArH), 2.27 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 156.2, 138.1, 131.4, 131.1, 130.9, 130.5, 130.2, 129.8, 129.3, 127.5, 117.7, 20.5; MS (ESI) *m/z* (%): 348 (47), 350 ([M + H]$^+$, 100), 352 (42); HRMS-ESI calcd for $C_{15}H_{13}{}^{35}ClN_3{}^{80}Se$: (M + H)$^+$: 349.9956; found: 349.9943.

5-(4-Chlorophenyl)-2-(4-methylphenylamino)-1,3,4-selenadiazole (**5i**): Yellow crystals; yield 71%; m.p. 203.3–204.5 °C; IR (KBr) (ν_{max} cm^{-1}): 3444, 1614, 1572, 1518, 1431, 1206, 1109, 1094, 832; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.43 (s, 1H, NH), 7.82 (d, *J* = 8.4 Hz, 2H, ArH), 7.63 (d, *J* = 8.4 Hz, 2H, ArH), 7.52 (d, *J* = 8.4 Hz, 2H, ArH), 7.15 (d, *J* = 8.4 Hz, 2H, ArH), 2.27 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.6, 159.8, 134.2, 131.1, 129.3, 128.9, 128.8, 127.0, 117.6, 117.0, 20.4; MS (ESI) *m/z* (%): 348 (46), 350 ([M + H]$^+$, 100), 352 (40); HRMS-ESI calcd for $C_{15}H_{13}{}^{35}ClN_3{}^{80}Se$: (M + H)$^+$: 349.9956; found: 349.9951.

5-(3-Methoxyphenyl)-2-(4-methylphenylamino)-1,3,4-selenadiazole (**5j**)**:** Yellow solid; yield 79%; m.p. 168.3–169.9 °C; IR (KBr) (ν_{max} cm^{-1}): 3443, 1602, 1568, 1431, 1285, 1109, 772, 682; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (t, *J* = 1.6 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H, ArH), 7.31–7.25 (m, 2H, ArH), 7.18 (d, *J* = 8.4 Hz, 2H, ArH), 6.96–6.93 (m, 1H, ArH), 3.86 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 161.5, 159.7, 139.0, 134.5, 133.8, 130.1, 129.8, 120.5, 119.0, 116.1, 111.8, 55.5, 21.0; MS (ESI) *m/z* (%): 344 (52), 346 ([M + H]$^+$, 100); HRMS-ESI calcd for $C_{16}H_{16}N_3O^{80}Se$: (M + H)$^+$: 346.0454; found: 346.0442.

5-(4-Methoxyphenyl)-2-(4-methylphenylamino)-1,3,4-selenadiazole (**5k**): Pink crystals; yield 80%; m.p. 198.7–199.5 °C; IR (KBr) (ν_{max} cm^{-1}): 3444, 1612, 1568, 1518, 1430, 1249, 1174, 1034, 828; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.31 (s, 1H, NH), 7.72 (d, *J* = 8.4 Hz, 2H, ArH), 7.52 (d, *J* = 7.6 Hz, 2H, ArH), 7.14 (d, *J* = 7.6 Hz, 2H, ArH), 7.01 (d, *J* = 8.4 Hz, 2H, ArH), 3.81 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.5, 162.3, 160.3, 138.3, 130. 8, 129.3, 128.8, 125.7, 117.4, 114.4, 55.3, 20.5; MS (ESI) *m/z* (%):

344 (50), 346 ([M + H]$^+$, 100); HRMS-ESI calcd for $C_{16}H_{16}N_3O^{80}Se$: (M + H)$^+$: 346.0454; found: 346.0445.

5-(4-Methylphenyl)-2-(4-methylphenylamino)-1,3,4-selenadiazole (**5l**): Pink solid; yield 78%; m.p. 188.4–189.8 °C; IR (KBr) (ν_{max} cm^{-1}): 3443, 1612, 1562, 1428, 1209, 1089, 805; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.40 (s, 1H, NH), 7.68 (d, *J* = 7.2 Hz, 2H, ArH), 7.53 (d, *J* = 6.4 Hz, 2H, ArH), 7.26 (d, *J* = 6.4 Hz, 2H, ArH), 7.14 (d, *J* = 7.2 Hz, 2H, ArH), 2.34 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.6, 158.2, 139.6, 138.4, 130.8, 130.5, 129.5, 129.2, 127.2, 117.5, 21.0, 20.5; MS (ESI) *m/z* (%): 328 (55), 330 ([M + H]$^+$, 100); HRMS-ESI calcd for $C_{16}H_{16}N_3{}^{80}Se$: (M + H)$^+$: 330.0504; found: 330.0493.

2-(4-Methoxyphenylamino)-5-(4-methylphenyl)-1,3,4-selenadiazole (**5m**): Yellow crystals; yield 81%; m.p. 158.7–159.8 °C; IR (KBr) (ν_{max} cm^{-1}): 3443, 1616, 1573, 1513, 1434, 1320, 1251, 1091, 1038, 808; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.28 (s, 1H, NH), 7.66 (d, *J* = 8.4 Hz, 2H, ArH), 7.56 (d, *J* = 8.8 Hz, 2H, ArH), 7.26 (d, *J* = 8.4 Hz, 2H, ArH), 6.93 (d, *J* = 8.8 Hz, 2H, ArH), 3.74 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, 154.4, 139.5, 130.5, 129.5, 127.1, 125.2, 119.2, 118.3, 114.1, 55.2, 21.0; MS (ESI) *m/z* (%): 344 (54), 346 ([M + H]$^+$, 100); HRMS-ESI calcd for $C_{16}H_{16}N_3O^{80}Se$: (M + H)$^+$: 346.0454; found: 346.0441.

5-(4-Methoxyphenyl)-2-(4-methoxyphenylamino)-1,3,4-selenadiazole (**5n**): Yellow crystals; yield 82%; m.p. 166.9–168.0 °C; IR (KBr) (ν_{max} cm^{-1}): 3052, 1622, 1574, 1513, 1433, 1253, 1172, 1030, 830, 778; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.30 (br s, 1H, NH), 7.72 (d, *J* = 8.8 Hz, 2H, ArH), 7.56 (d, *J* = 8.8 Hz, 2H, ArH), 7.01 (d, *J* = 8.8 Hz, 2H, ArH), 6.93 (d, *J* = 8.8 Hz, 2H, ArH), 3.81 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.6, 154.5, 134.3, 133.1, 129.7, 129.0, 127.3, 127.2, 119.3, 114.1, 55.3, 55.2; MS (ESI) *m/z* (%): 360 (40), 362 ([M + H]$^+$, 100); HRMS-ESI calcd for $C_{16}H_{16}N_3O_2{}^{80}Se$: (M + H)$^+$: 362.0403; found: 362.0391.

5-(4-Chlorophenyl)-2-(4-methoxyphenylamino)-1,3,4-selenadiazole (**5o**): Yellow crystals; yield 74%; m.p. 203.3–204.5 °C (lit.[15] 205–206 °C); IR (KBr) (ν_{max} cm^{-1}): 3444, 1614, 1572, 1518, 1431, 1206, 1109, 1094, 832; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.36 (s, 1H, NH), 7.81 (d, *J* = 8.4 Hz, 2H, ArH), 7.57 (d, *J* = 8.8 Hz, 2H, ArH), 7.53 (d, *J* = 8.4 Hz, 2H, ArH), 6.94 (d, *J* = 8.8 Hz, 2H, ArH), 3.74 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.0, 154.5, 134.0, 132.0, 128.9, 128.6, 127.9, 119.3, 118.5, 114.1, 55.2; MS (ESI) *m/z* (%): 364 (50), 366 ([M + H]$^+$, 100), 368 (51); HRMS-ESI calcd for $C_{15}H_{13}ClN_3O^{80}Se$ (M + H)$^+$: 365.9905; found: 365.9907.

2-Cyclohexylamino-5-phenyl-1,3,4-selenadiazole (**5p**): White solid; yield 60%; m.p. 155.9–156.8 °C; IR (KBr) (ν_{max} cm^{-1}): 3163, 1564, 1437, 1363, 1261, 1055, 958, 889, 761, 688; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.97 (d, *J* =7.2 Hz, 1H, ArH), 7.70–7.68 (m, 2H, ArH), 7.44–7.39 (m, 3H, 2ArH, NH), 3.65–3.57 (m, 1H, CH), 2.01–1.99 (m, 2H, CH_2), 1.74–1.70 (m, 2H, CH_2), 1.59–1.55 (m, 1H, CH_2), 1.39–1.16 (m, 5H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.3, 159.8, 133.4, 128.6, 128.3, 126.5, 54.2, 31.7, 24.9, 23.9; ESI-MS *m/z* (%): 306 (46), 308 ([M + H]$^+$, 100); HRMS-ESI calcd for $C_{14}H_{18}N_3{}^{80}Se$: (M + H)$^+$: 308.0661; found: 308.0662.

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Electronic Supplementary Information

The HRMS data of **5p** are available through: stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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