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Reactions of selenazadienes with chloroacetonitrile yielded 1,3-selenazol-5-carbonitriles in moderate to high yields. Reactions of the selenazadienes with chloroacetyl chloride and then with amines gave 1,3-selenazole-5-carboxamides.

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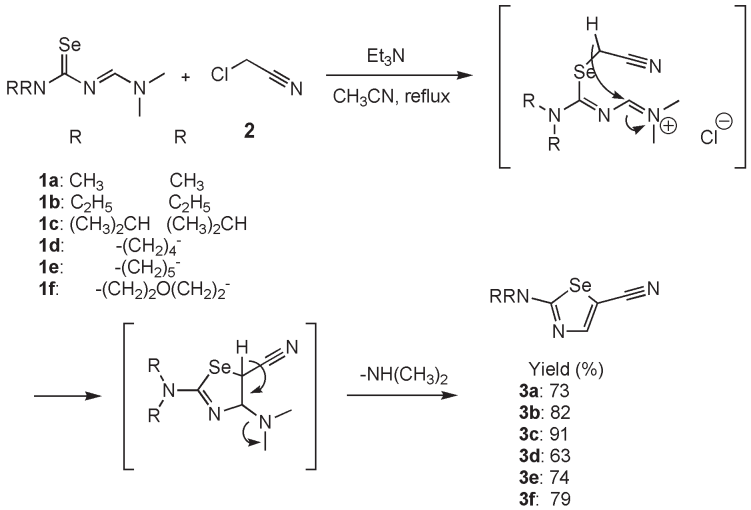
Syntheses of 1,3-selenazoles have been extensively studied, not only because of strong interest in these compounds as synthetic tools [1] but also as a result of their biological activities [2]. Many reports on the synthesis of 1,3-selenazole use selenoamide [3] or selenourea [4] as the starting material. Recently, we have reported that use of selenazadiene as the precursor provides one of the efficient methods for the synthesis of 1,3-selenazole. Reaction of selenazadiene with dimethyl acetylenedicarboxylate (DMAD) affords a 4*H*-selenazine, six-membered ring compound that converts to a 4*H*-selenopyran by cycloreversion and recycloaddition with excess DMAD. Reaction of selenoazadienes with chloroacetyl chloride gave 1,3-selenazole-5-carboxylic acids or 1,3-selenazol-5-carboxylates [5]. Herein, we further describe the syntheses of other kinds of 1,3-selenazoles using selenazadienes.

Selenazadienes **1** were prepared by a modification of the reported experimental conditions that were used for synthesis of *N*-thioacylamidine from thiobenzamides [6]. Condensation of *N*,*N*-unsubstituted selenoureas with *N*,*N*-dimethylformamide dimethylacetal (1.5 equiv.) at room temperature for 6 h led to high yields of six different selenazadienes **1**. The synthesis of 2-piperidino-1,3-selenazole-5-carbonitrile **3e** from *N*,*N*-dimethyl-*N*'-(1-piperidinoselenocarbonyl)formamidine **1e** and chloroacetonitrile **2** under various conditions to establish the optimal conditions in the presence of triethylamine. When the reaction was carried out in THF solution or acetonitrile, the yield of **3e** was 31 or 74%, respectively. The reaction without triethylamine in acetonitrile gave **3e** in 53% yield. Under the optimal reaction conditions, six kinds of 1,3-selenazole-5-carbonitriles **3a-f** were prepared by reactions of selenazadienes **1a-f** with chloroacetonitrile **2** in the presence of triethylamine (Scheme 1).

The structure of **3** was confirmed by studies of IR, MS, ^{1}H, ^{13}C, ^{77}Se NMR spectra and elemental analysis. The structure of **3e** was also determined using X-ray diffraction analysis (Figure 1) [7]. The bond angle of the selenium atom C5-Se1-C2 was 83.52(12)°, consistent with the previous reported value [8]. The bond length of C2-N3 in **3e** is 1.313(3) Å and clearly shows that it is a double bond. The bond lengths of N3-C4 (1.358(4) Å), C5-C6 (1.417(4) Å) and C2-N8 (1.346(4) Å) in **3e** are shorter than the usual single bond length of 1.47 Å [9].

Scheme 1



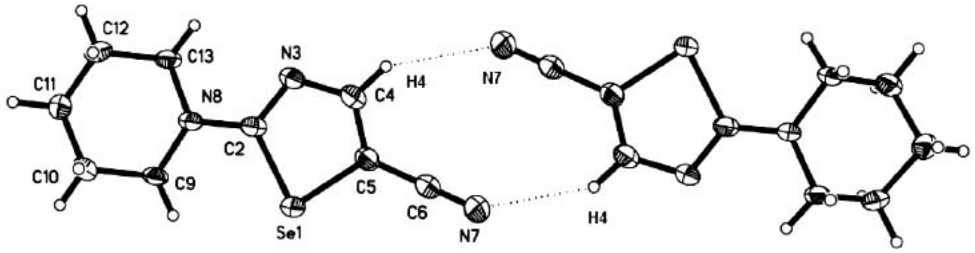
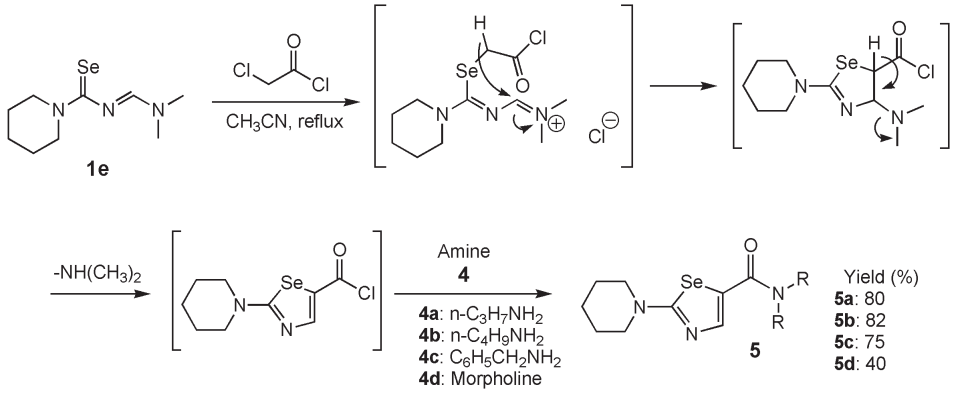


Figure 1. ORTEP diagram (50% thermal ellipsoids) of compound **3e**.

Previously, we reported the syntheses of 1,3-selenazol-5-carboxylate by reactions of selenoazadienes **1** with chloroacetyl chloride and then with alcohol. We now examined subsequent reactions with amines **4** under similar conditions. The resulting acyl chloride intermediates were trapped by amines **4** to yield the corresponding amides **5** in moderate to high yields (Scheme 2).

Scheme 2



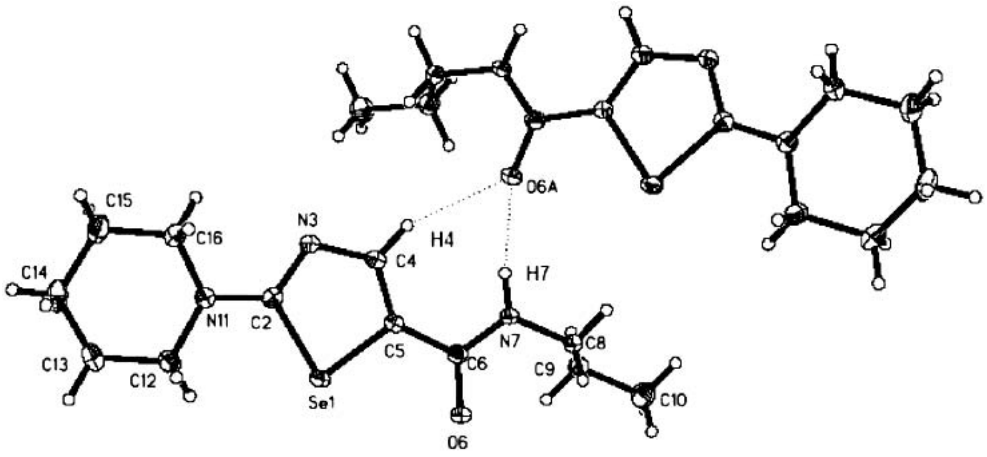


Figure 2. ORTEP diagram (50% thermal ellipsoids) of compound **5a**.

The structure of **5** was confirmed by studies of IR, MS, ^{1}H, ^{13}C, ^{77}Se NMR spectra and elemental analysis. The molecular structure of **5a** was definitively determined using X-ray diffraction analysis (Figure 2). The atomic intervals between O6 and N7 and between O6 and C4 are 2.874(3) and 3.255(4) Å, respectively. We made comparison between structure features of **3e** bearing cyano moiety and **5a** bearing amide moiety. The bond lengths of C4-N3 (1.358(4) Å), C2-C8 (1.346(4) Å) and C5-C6 (1.417(4) Å) in **3e** are shorter than the bond lengths of C4-N3 (1.377(4) Å), C2-C11 (1.354(4) Å) and C5-C6 (1.466(4) Å) in **5a**. This result can be attributed to delocalization of the π electrons and lone pair electrons on the nitrile group.

Hence, selenazadienes are confirmed to be useful as starting material for the synthesis of selenium-containing heterocyclic 1,3-selenazoles.

EXPERIMENTAL

General Procedure for Synthesis of 2-Dimethylamino-1,3-selenazole-5-carbonitrile (**3a**).

Chloroacetonitrile (0.063 mL, 1.0 mmol) was added to a stirred solution of *N*,*N*-dimethyl-*N'*-(dimethylaminoselenocarbonyl)formamidine **1a** (100 mg, 0.5 mmol) in dry THF (7 mL) at room temperature under an argon atmosphere. The reaction mixture was refluxed for 3 h. Then triethylamine (0.17 mL, 1.2 mmol) was added into the reaction mixture, and then the mixture was refluxed for 4 h. The mixture was extracted with diethyl ether and washed with water. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with hexane/diethyl ether (1/5) as the eluent to give **3a** (147 mg, 73%) as colorless crystals; Mp: 88.2-88.5 ºC, IR (KBr): 2193 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.18 (s, 6H, CH_3), 7.65 (s, 1H, CH), ^{13}C NMR (125 MHz, $CDCl_3$): δ 41.5, 94.0, 115.7, 153.1, 177.1, ^{77}Se NMR (95 MHz, $CDCl_3$): δ 586.3, MS (CI): *m/z* = 202 [M^++1].

Anal. Calcd. for $C_6H_7N_3Se$: C, 36.01; H, 3.53; N, 21.00. Found: C, 36.32; H, 3.47; N, 21.05.

2-Diethylamino-1,3-selenazole-5-carbonitrile (**3b**).

This compound was obtained as colorless crystals; Mp: 46.0-46.8 ºC, IR (KBr): 2197 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 1.28 (t, *J* =7.2 Hz, 6H, CH_3), 3.50 (q, *J* =7.2 Hz, 4H, CH_2), 7.61 (s, 1H, CH), ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.3, 47.6, 92.8, 115.9, 153.1, 175.5, ^{77}Se NMR (95 MHz, $CDCl_3$): δ 583.5, MS (CI): *m/z* = 230 [M^++1].

Anal. Calcd for $C_8H_{11}N_3Se$: C, 42.12; H, 4.86; N, 18.42. Found: C, 41.93; H, 4.79; N, 18.15.

2-Diisopropylamino-1,3-selenazole-5-carbonitrile (**3c**).

This compound was obtained as pale yellow crystals; Mp: 148.9-149.5 ºC, IR (KBr): 2191 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 1.41 (d, *J* =6.9 Hz, 12H, CH_3), 3.67-3.71 (m, 2H, CH), 7.60 (s, 1H, CH), ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.9, 29.7, 92.0, 116.4, 153.1, 173.9, ^{77}Se NMR (95 MHz, $CDCl_3$): δ 598.1, MS (CI): *m/z* = 259 [M^++1].

2-Pyrrolidino-1,3-selenazole-5-carbonitrile (**3d**).

This compound was obtained as pale yellow crystals; Mp: 118.0-118.8 ºC, IR (KBr): 2195 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 2.12 (t, *J* =6.9 Hz, 4H, CH_2), 3.48 (m, 4H, CH_2), 7.67 (s, 1H, CH), ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.6, 51.2, 93.2, 115.9, 153.1, 173.1, ^{77}Se NMR (95 MHz, $CDCl_3$): δ 580.8, MS (CI): *m/z* = 228 [M^++1].

Anal. Calcd. for $C_{10}H_{15}N_3Se$: C, 46.88; H, 5.90; N, 16.40. Found: C, 46.76; H, 5.86; N, 16.31.

2-Piperidino-1,3-selenazole-5-carbonitrile (3e).

This compound was obtained as pale yellow crystals; Mp: 96.2-96.5 ºC, IR (KBr): 2196 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 1.70-1.71 (m, 6H, CH_2), 3.51-3.53 (m, 4H, CH_2), 7.60 (s, 1H, CH), ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.9, 25.1, 51.4, 93.5, 115.9, 153.1, 177.0, ^{77}Se NMR (95 MHz, $CDCl_3$): δ 587.6, MS (CI): *m/z* = 242 [M^++1].

Anal. Calcd. for $C_9H_{11}N_3Se$: C, 45.01; H, 4.62; N, 17.50. Found: C, 45.19; H, 4.77; N, 17.55.

X-ray Crystallographic Data.

Single crystals were grown from CH_2Cl_2-hexane. Crystal system Triclinic; Space group *P*-1; T = 190(2) K; a = 6.3947(6) Å, b = 9.0243(9) Å, c = 9.1054(9) Å, α = 89.284(5)°, β = 75.010(5)°, γ = 73.645(5)°, V = 486.00(8) $Å^3$, *Z* = 2; D_c = 1.641 g cm^{-3}; Crystal size 0.10 x 0.09 x 0.02 mm; *θ* range for data collection 3.2 to 27.5°, Limiting indices $-8 \le h \le 8$, $-11 \le k \le 11$, $-11 \le l \le 11$; Reflections collected: 8500, Independent reflections: 2242 [R_{int} = 0.0259]; Refinement method: Full-matrix least-squares on F^2, Goodness of fit on F^2: 1.068, Final *R* indices [$I>2\sigma(I)$] *R*1 = 0.0334, *wR*2 = 0.0707 *R* indices (all data) *R*1 = 0.0537, *wR*2 = 0.0772, Largest diff. peak and hole 0.404 and -0.353 e. $Å^{-3}$; Selected bond lengths (Å) and angles (°), Se(1)-C(2): 1.899(3), N(3)-C(2): 1.313(3), C(4)-N(3): 1.358(4), C(5)-C(4): 1.350(4), Se(1)-C(5): 1.878(3), C(2)-N(8): 1.346(4), C(5)-C(6): 1.417(4), C(6)-N(7): 1.141(4), C(5)-Se(1)-C(2) 83.52(12), N(7)-C(6)-C(5): 179.3(3) for all data [7].

2-Morpholino-1,3-selenazole-5-carbonitrile (**3f**).

This compound was obtained as pale yellow solid; Mp: 78.5-79.5 ºC, IR (KBr): 2201 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 3.55 (t, *J* =5.2 Hz, 4H, CH_2), 3.82 (t, *J* =5.2 Hz, 4H, CH_2), 7.65 (s, 1H, CH), ^{13}C NMR (125 MHz, $CDCl_3$): δ 49.8, 65.8, 95.0, 115.3, 152.7, 177.5, ^{77}Se NMR (95 MHz, $CDCl_3$): δ 597.0, MS (CI): *m/z* = 244 [M^++1].

Anal. Calcd. for $C_8H_9N_3OSe$: C, 39.68; H, 3.75; N, 17.35. Found: C, 39.54; H, 3.76; N, 17.42.

Synthesis of *N*-Propyl-2-piperidino-1,3-selenazole-5-carboxamide (**5a**).

Chloroacetyl chloride (0.16 mL, 2.0 mmol) was added to a stirred solution of *N*,*N*-dimethyl-*N'*-(piperidinoselenocarbonyl)-formamidine **1e** (250 mg, 1.0 mmol) in dry THF (20 mL) at room temperature under an argon atmosphere. The reaction mixture was refluxed for 48 h. After *n*-propylamine (0.16 mL, 2.0 mmol) was added, the resulting mixture was refluxed for 5 min. The mixture was extracted with ethyl acetate and washed with aqueous saturated sodium carbonate. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with dichloromethane/methanol (20/1) as the eluent to give **5a** (240 mg, 80%) as orange crystals; Mp: 179.2-180.6 ºC, IR (KBr): 1603 cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6): δ 0.86 (t, *J* =7.3 Hz, 3H), 1.47 (m, *2*H), 1.58 (s, 6H), 3.11 (q, *J* =6.6 Hz, 2H), 3.44 (s, 4H), 7.68 (s, 1H), 8.09 (t, *J* =5.4 Hz, 1H), ^{13}C NMR (125 MHz, DMSO-d_6): δ 11.5, 22.6, 23.6, 24.8, 40.8, 50.2, 127.5, 142.5, 162.1, 175.1, ^{77}Se NMR (95 MHz, DMSO-d_6): δ 541.1. MS (CI): *m/z* = 302 [M^++1].

Anal. Calcd. for $C_{12}H_{19}N_3OSe$: C, 48.00; H, 6.38; N, 13.99. Found: C, 48.01; H, 6.36; N, 14.21.

X-ray Crystallographic Data.

Single crystals were grown from CH_2Cl_2-hexane. Crystal system Orthorhombic; Space group *Pbca*; T = 190(2) K; a = 9.9619(10) Å, b = 14.8053(15) Å, c = 17.9751(18) Å, V = 2651.1(5) $Å^3$, *Z* = 8; D_c = 1.505 g cm^{-3}; Crystal size 0.26 x 0.10 x 0.08 mm; *θ* range for data collection 3.0 to 27.5°, Limiting indices $-12 \le h \le 12$, $-19 \le k \le 19$, $-23 \le l \le 23$; Reflections

collected: 34724, Independent reflections: 3039 [R_{int} = 0.0580]; Refinement method: Full-matrix least-squares on F^2, Goodness of fit on F^2: 1.029, Final R indices [$I>2\sigma(I)$] $R1$ = 0.0367, $wR2$ = 0.0802, R indices (all data) $R1$ = 0.0605, $wR2$ = 0.0892, Largest diff. peak and hole 0.455 and -0.487 e. Å^{-3}; Selected bond lengths (Å) and angles (°), Se(1)-C(2): 1.898(3), N(3)-C(2): 1.313(4), C(4)-N(3): 1.377(4), C(5)-C(4): 1.350(4), Se(1)-C(5): 1.876(3), C(2)-N(11): 1.354(4), C(5)-C(6): 1.466(4), C(6)-N(7): 1.336(3), C(5)-Se(1)-C(2) 84.41(12) for all data [7].

N-Butyl-2-piperidino-1,3-selenazole-5-carboxamide (**5b**).

This compound was obtained as colorless crystals; Mp: 107.9-109.1 ºC, IR (KBr): 1609 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.89 (t, J =7.4 Hz, 3H), 1.30 (m, *2*H), 1.45 (quint, J =7.4 Hz, 2H), 1.50 (s, 6H), 3.16 (q, J =6.7 Hz, 2H), 3.44 (s, 4H), 7.68 (s, 1H), 8.07 (t, J =5.4 Hz, 1H), ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.7, 19.6, 23.6, 24.8, 31.5, 38.7, 50.2, 127.5, 142.4, 162.1, 175.1, ^{77}Se NMR (95 MHz, DMSO-d_6): δ 541.1, MS (CI): *m/z* = 316 [M$^+$+1].

Anal. Calcd. for $C_{13}H_{21}N_3OSe$: C, 49.66; H, 6.73; N, 13.37. Found: C, 49.51; H, 6.57; N, 13.32.

N-Benzyl-2-piperidino-1,3-selenazole-5-carboxamide (**5c**).

This compound was obtained as orange crystals; Mp: 141.0-142.0 ºC, IR (KBr): 1611 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.59 (s, 6H), 3.45 (s, 4H), 4.39 (s, 2H), 7.22-7.40 (m, 5H), 7.76 (s, 1H), 8.67 (t, J =5.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.6, 24.8, 42.3, 50.2, 126.7, 127.2, 128.3, 143.0, 162.2, 175.2, ^{77}Se NMR (95 MHz, DMSO-d_6): δ 540.7, MS (CI): *m/z* = 351 [M$^+$+1].

Anal. Calcd. for $C_{16}H_{18}N_3OSe$: C, 55.33; H, 5.22; N, 12.10. Found: C, 55.17; H, 5.21; N, 12.08.

5-(1-Morpholinocarbonyl)-2-piperidino-1,3-selenazole (**5d**).

This compound was obtained as pale yellow crystals; Mp: 87.5-89.3 ºC, IR (KBr): 1591 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.59-1.61 (m, 6H), 3.04-3.06 (m, 4H), 3.45 (s, 4H), 3.60 (s, 4H), 7.48 (s, 1H), ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.5, 24.7, 45.5, 50.1, 66.1, 126.8, 143.8, 163.2, 174.7, ^{77}Se NMR (95 MHz, DMSO-d_6): δ 568.5, MS (CI): *m/z* = 331 [M$^+$+1].

Anal. Calcd. for $C_{13}H_{19}N_3O_2Se$: C, 47.57; H, 5.83; N, 12.80. Found: C, 47.42; H, 5.77; N, 12.72.

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[7] Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication, CCDC No. 251943 for **3e** and CCDC No. 251944 for **5a**. Copies of this information can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: + 44 1233 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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