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ONE-POT SYNTHESIS OF 2-IMINO-1,3-SELENAZOLIDINES BY REACTION OF ISOSELENOCYANATES WITH PROPARGYLAMINE

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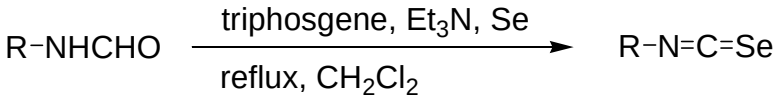
Abstract – One-pot synthesis of 2-imino-5-methylene-1,3-selenazolidines has been achieved by reactions of alkylisoselenocyanates with propargylamines in high yields. ^{1}H NMR and NOESY experiments were used to explain the selenium coupling with hydrogen of carbon-carbon double bond.

INTRODUCTION

1,3-Selenazole derivatives, selenium-nitrogen heterocycles, have enthusiastically been studied in the fields of chemistry and pharmaceutical science, because they biologically act as antioxidants, can protect oxidant-induced DNA damage and inhibit inducible nitric oxide production.[1] Therefore, several researchers have put in efforts to develop synthetic methods of 1,3-selenazole derivatives. For the synthesis of the 1,3-selenazole, several selenating reagents have been used such as selenoamides,[2] selenoureas[3] and selenazadienes.[4] In contrast, the chemistry of heterocycles using isoselenocyanates has been limited. Recently, heterocycles such as 1,3-selenazolidines, perhydro-1,3-selenazines and 1,3-selenazoles have been synthesized by reactions using alkyl isoselenocyanates.[5] Use of isoselenocyanates are one of the efficient methods for the synthesis of 1,3-selenazole derivatives. Herein, we describe one-pot synthesis of 2-imino-1,3-selenazolidines and their characterization.

RESULTS AND DISCUSSION

The alkyl and aryl isoselenocyanates **(1)** were prepared by reactions of *N*-substituted formamides with an excess of triphosgene, selenium and triethylamine (Scheme 1).[6]



1

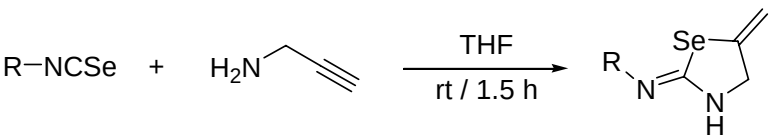
R	Yield / %
p-$CH_3C_6H_4$	94% **(1a)**
C_6H_5	96% **(1b)**
p-ClC_6H_4	72% **(1c)**
Naphthyl	92% **(1d)**
Benzyl	89% **(1e)**
cyclo-C_6H_{11}	30% **(1f)**

Scheme 1

Reaction of isoselenocyanate **(1)** with propargylamine was carried out at room temperature for 1.5 h to afford 2-imino-5-methylidene-1,3-selenazolidine **(2)** (Scheme 2).

The structure of **2a** was elucidated by studies of IR, ^{1}H-, ^{13}C-, ^{77}Se-NMR, COSY, HMQC, HMBC and NOESY, MS, HRMS, elemental analysis and X-ray analysis. Under the similar reaction conditions, the reactions of six kinds of isoselenocyanates **(1)** with propargylamine gave the 2-imino-5-methylidene-1,3-selenazolidines **(2)** in excellent yields (Table 1). Both alkyl and aryl isoselenocyanates provided the corresponding 2-imino-5-methylidene-1,3-selenazolidines **(2)** in excellent yields. The structures of products **(2b-2f)** were determined by comparing the spectral data with those of **2a**.

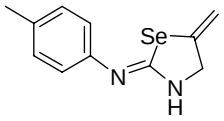
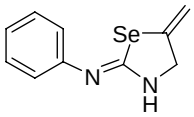
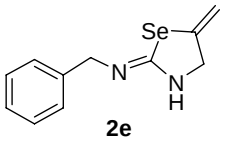
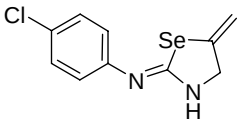
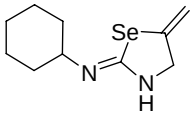
In the ^{1}H NMR spectra of **2a** in $CDCl_3$, an interesting spectral feature was observed. This was the selenium coupling with the H_{5b} proton $^3J(^{77}Se\text{-}^1H)$ = 23.9 Hz, but the same coupling was not observed with H_{5a} proton. The H_{5b} proton is more downfield as compared to the H_{5a} proton (Figure 1). In order to determine the complete assignment of protons, 1D NOE and NOESY experiments were carried out. The



1 **2**

Scheme 2

Table 1. Reaction of alkyl isoselenocyanates with propargylamine

Product (**2**)	Yield (%)[a]	^{77}Se NMR (δ)	Product (**2**)	Yield (%)[a]	^{77}Se NMR (δ)
 **2a**	89	435.8	 **2d**	88	434.9
 **2b**	96	435.6	 **2e**	85	481.4
 **2c**	97	429.0	 **2f**	93	479.8

a: Isolated yield.

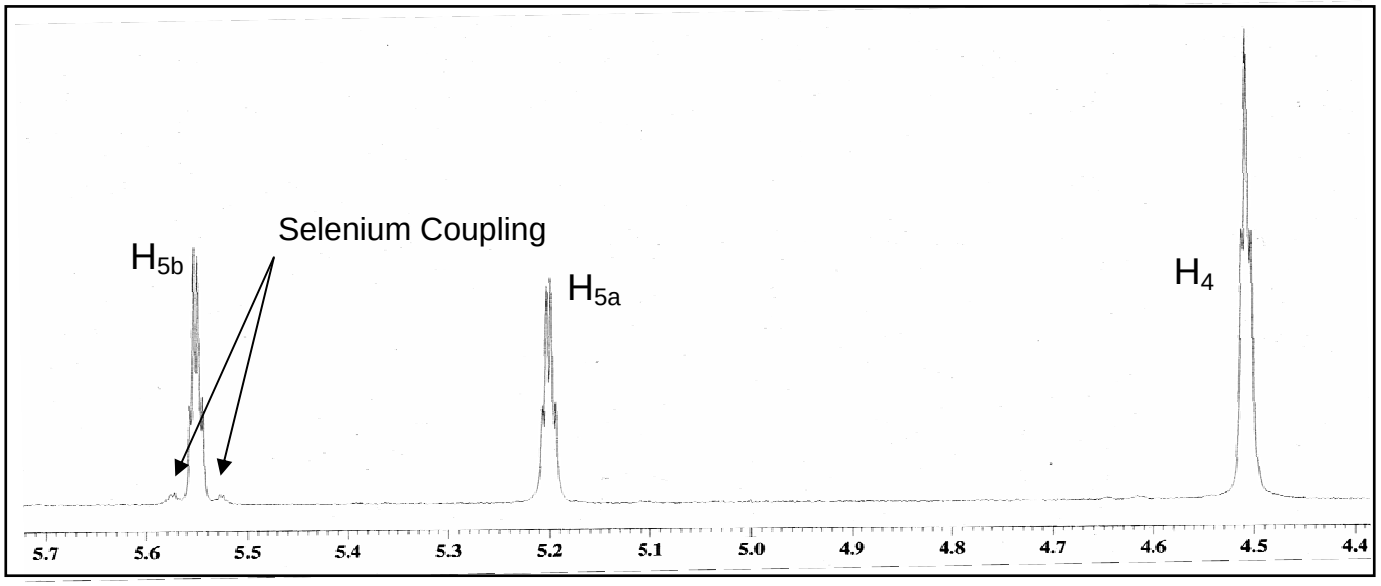


Figure 1. ^{1}H NMR of **2a**

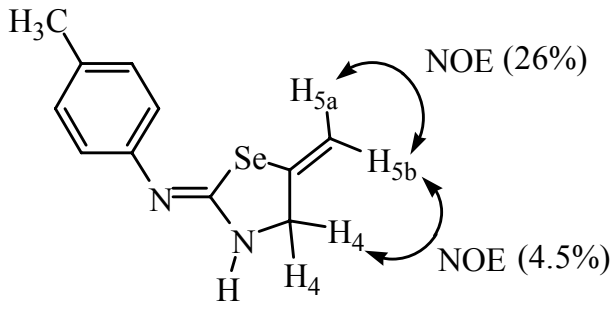


Figure 2

NOE experiment of compound **(2a)** showed, the NOE of H_{5a} proton with H_{5b} (26%) and NOE of H_{5b} proton with H_4 protons (4.5%) (Figure 2). From the above results it is clear that selenium shows coupling with the trans-proton. We feel that these regularities, if found to be general, may be an important aid for determining structures and conformations of organoselenium compounds for which such NMR information is not available. In the ^{77}Se NMR spectra of the 1,3-selenazolidines **(2)**, ^{77}Se signals were observed in the range of δ 449.4±24.3, which are at a higher field as compared with ^{77}Se signals of selenocarbonyl compounds (δ 1420-2131).[7] The values are typical for a C-Se single bond with an sp^3 selenium atom not for a C=Se double bond with an sp^2 selenium atom.[8] Fujiwara et al. reported the synthesis of 5-alkylideneselenazolin-2-one by the reaction of 3-aminoalkynes with carbon monoxide and selenium, in which the rate of the reaction is accelerated by the addition of a proton source.[9] But in the present reaction the additional proton source is infact not needed.

In order to confirm the structure of **2a**, we carried out the X-Ray analysis of this compound. An ORTEP drawing, depicted in Figure 3, shows the molecular structure of the **2a**.[10] The bond angle the selenium atom C1-Se1-C3 was 87.4(2)°, consistent with the previous reported value.[11] The bond lengths of C1-N2 and C3-C11in **2a** are 1.291(7) Å and 1.312(10) Å respectively and clearly shows that these are the double bonds. The two C-N bond lengths of both N1-C1 (1.345(7) Å) and N1-C2 (1.428(8) Å) in **2a** are shorter than the usual single bond length of 1.47 Å.[12] There are no significant geometric differences between the molecules, except the orientation of the phenyl rings. Each of the independent molecules forms a centrosymmetric hydrogen-bonded dimer. Hydrogen-bond distances are similar in both independent dimers. Compound **(2a)** possesses an exocyclic carbon-nitrogen double bond with *Z*-configuration. The five-membered ring is planar.

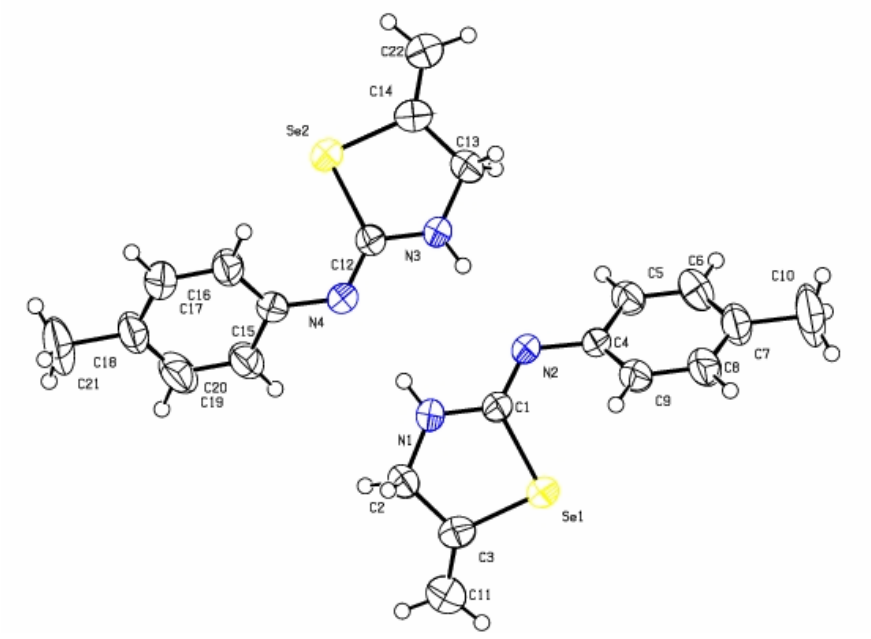
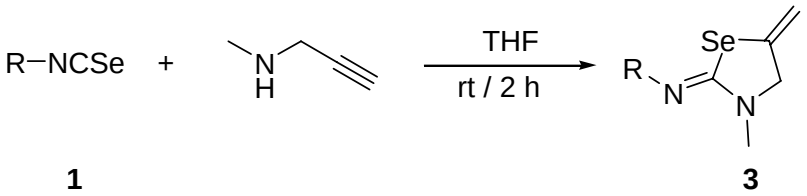


Figure 3. X-Ray-crystal structure of **2a**

Next, the effect of substituent at the amine nitrogen was examined. Reaction of isoselenocyanate **(1)** with *N*-methylpropargylamine was carried out to afford 2-imino-3-methyl-5-methylidene-1,3-selenazolidine **(3)** (Scheme 4).

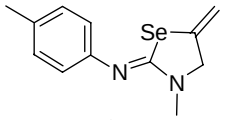
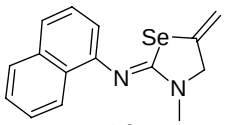
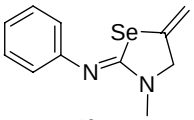
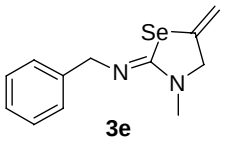
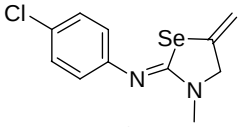
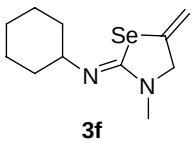


1 **3**

Scheme 4

Reactions of six kinds of alkyl isoselenocyanates **(1)** with *N*-methylpropargylamine were carried out at room temperature for 2 h. Purification of the reaction mixture by silica gel column chromatography afforded the 2-imino-3-methyl-5-methylidene-1,3-selenazolidines **(3)** in high yields (Table 2). In the ^{77}Se NMR spectra of the 3-methyl-1,3-selenazolidines **(3)**, ^{77}Se signals were observed in the range of δ 410.6±10.6. The reactions of primary amines gave higher yields as compared to the secondary amine.

Table 2. Reaction of alkyl isoselenocyanates with *N*-methylpropargylamine

Product (**3**)	Yield (%)[a]	^{77}Se NMR (δ)	Product (**3**)	Yield (%)[a]	^{77}Se NMR (δ)
 **3a**	65	414.9	 **3d**	78	419.6
 **3b**	76	415.6	 **3e**	72	403.6
 **3c**	71	417.7	 **3f**	73	392.1

a: Isolated yield.

In conclusion, we have demonstrated a one-pot synthesis of 2-imino-5-methylidene-1,3-selenazolidines by reactions of the acyl isoselenocyanates **(1)** with propargylamine.

EXPERIMENTAL

General

The chemical shifts of ^{77}Se NMR were expressed in ppm deshielded with respect to neat Me_2Se in $CDCl_3$. $^3J(^{77}Se\text{-}^1H)$ values are the satellites of the ^{1}H NMR spectra.

Synthesis of 2-(4-methylphenyl)imino-5-methylene-1,3-selenazolidine (2a). To a solution of 4-Methylphenylisoselenocyanate (98.1 mg, 0.50 mmol) in dry THF (8.0 mL), propargylamine (48 μL, 0.75 mmol) was added. The mixture was stirred at ambient for 1.5 h. The reaction mixture was extracted with diethylether and washed with water. The combined organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with ethyl acetate:n-hexane (1:3) as the eluent to give **2a** (112.4 mg, yield 89%). mp 82.0-83.0 °C; IR (KBr): 1629, 1549 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (3H, s, CH_3), 4.51 (2H, t, J = 1.9 Hz, CH_2), 5.19 (1H, dd, J = 2.9, 3.8 Hz, =CH_2), 5.53 (1H, dd, J = 1.9, 3.8 Hz, $^3J(^{77}Se\text{-}^1H)$ = 23.9 Hz, =CH_2), 6.98 (2H, d, J = 7.7 Hz, Ar), 7.08 (2H, d, J = 7.7 Hz, Ar), (9.29 (1H, br, NH), at -60°C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 59.3, 108.8, 121.2, 129.6, 133.4, 143.4, 145.0, 157.8; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 435.8; MS (FAB): *m/z* = 253 [M^++1]; Anal. Calcd for $C_{11}H_{12}N_2Se$: C, 52.60; H, 4.82; N, 11.15. Found: C, 52.55; H, 4.85; N, 10.79.

2-Phenylimino-5-methylene-1,3-selenazolidine (2b) mp 83.9-84.6 °C; IR (KBr): 1618, 1553 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, -40°C): δ 4.46 (2H, s, CH_2), 5.23 (1H, d, J = 2.3 Hz, =CH_2), 5.58 (1H, d, J = 1.7 Hz, $^3J(^{77}Se\text{-}^1H)$ = 24.6 Hz, =CH_2), 7.08 (2H, d, J = 7.5 Hz, Ar), 7.13 (1H, t, J = 7.5 Hz, Ar), 7.33 (2H, d, J = 7.5 Hz, Ar), 8.27 (1H, br, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 58.7, 108.9, 121.2, 123.7, 129.1, 142.9, 147.8, 158.0; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 435.6; MS (CI): *m/z* = 239 [M^++1]; Anal. Calcd for $C_{10}H_{10}N_2Se$: C, 50.64; H, 4.25; N, 11.81. Found: C, 50.70; H, 4.34; N, 11.60.

2-(4-Chlorophenyl)imino-5-methylene-1,3-selenazolidine (2c) mp 125.7-126.2 °C; IR (KBr): 1646, 1583 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, -40℃): δ 4.38 (2H, s, CH_2), 5.24 (1H, d, J = 1.7 Hz, =CH_2), 5.58 (1H, d, J = 1.7 Hz, $^3J(^{77}Se\text{-}^1H)$ = 24.6 Hz, =CH_2), 6.96 (2H, d, J = 8.6 Hz, Ar), 7.26 (2H, d, J = 8.6 Hz, Ar), 8.99 (1H, br, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 57.2, 109.6, 122.5, 128.9, 129.1, 141.5, 147.3, 158.7; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 429.0; MS (EI): *m/z* = 272 [M^+]; Anal. Calcd for $C_{10}H_9ClN_2Se$: C, 44.22; H, 3.34; N, 10.31. Found: C, 44.48; H, 3.32; N, 10.32.

2-(2-Naphthyl)imino-5-methylene-1,3-selenazolidine (2d) mp 147.9-148.2 °C; IR (KBr): 1623, 1558 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.49 (2H, t, J = 2.3 Hz, CH_2), 5.21 (1H, dd, J = 2.3, 4.6 Hz, =CH_2), 5.56 (1H, dd, J = 2.3, 4.0 Hz, $^3J(^{77}Se\text{-}^1H)$ = 25.0 Hz, =CH_2), 7.21 (1H, dd, J = 2.3, 8.6 Hz, Ar), 7.33-7.47 (2H, m, Ar), 7.54 (1H, d, J = 1.1 Hz, Ar), 7.71-7.82 (3H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 58.3,

109.2, 117.0, 122.2, 124.6, 126.2, 127.3, 127.6, 129.0, 130.6, 134.1, 142.5, 145.9, 158.0; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 434.9; MS (EI): *m/z* = 288 [M^+]; Anal. Calcd for $C_{14}H_{12}N_2Se$: C, 58.54; H, 4.21; N, 9.75. Found: C, 58.57; H, 4.29; N, 9.25.

2-Benzylimino-5-methylene-1,3-selenazolidine (2e) mp 109.3-109.5 °C; IR (KBr): 1607, 1515 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.41 (2H, s, CH_2), 4.64 (2H, t, *J* = 2.3 Hz, CH_2), 5.16 (1H, dd, *J* = 2.3, 4.0 Hz, =CH_2), 5.48 (1H, dd, *J* = 2.3, 4.0 Hz, $^3J(^{77}Se\text{-}^1H)$ = 25.8 Hz, =CH_2), 7.20-7.38 (5H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 49.1, 69.7, 107.1, 127.4, 127.6, 128.5, 138.2, 150.5, 155.1; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 481.4; MS (FAB): *m/z* = 253 [M^++1]; Anal. Calcd for $C_{11}H_{12}N_2Se$: C, 52.60; H, 4.82; N, 11.15. Found: C, 53.02; H, 4.85; N, 11.13.

2-Cyclohexylimino-5-methylene-1,3-selenazolidine (2f) mp 160.1-161.0 °C; IR (KBr): 1624, 1538 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12-1.41 (5H, m, ringCH_2), 1.55-1.75 (3H, m, ringCH_2), 1.98-2.07 (2H, m, ringCH_2), 3.42-3.51 (1H, m, ringCH), 4.49 (1H, br, NH), 4.69 (2H, t, *J* = 2.3 Hz, CH_2), 5.17 (1H, dd, *J* = 2.3, 4.0 Hz, =CH_2), 5.49 (1H, dd, *J* = 2.3, 4.0 Hz, $^3J(^{77}Se\text{-}^1H)$ = 25.0 Hz, =CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.8, 25.5, 33.6, 53.9, 70.2, 106.9, 150.8, 153.9; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 479.8; MS (CI): *m/z* = 245 [M^++1]; Anal. Calcd for $C_{10}H_{16}N_2Se$: C, 49.38; H, 6.63; N, 11.52. Found: C, 49.05; H, 6.52; N, 11.20.

2-(4-Methylphenyl)-3-methyl-5-methylene-1,3-selenazolidine (3a) IR (neat): 1614 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.22 (3H, s, CH_3), 3.00 (3H, s, CH_3), 4.15 (2H, t, *J* = 2.3 Hz, CH_2), 5.11 (1H, dd, *J* = 2.3, 4.0 Hz, =CH_2), 5.48 (1H, dd, *J* = 1.7, 4.0 Hz, $^3J(^{77}Se\text{-}^1H)$ = 23.5 Hz, =CH_2), 6.74 (2H, d, *J* = 8.0 Hz, Ar), 6.99 (2H, d, *J* = 8.0 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 33.7, 60.4, 109.6, 121.4, 129.5, 132.8, 136.5, 150.5, 155.5; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 414.9; MS (EI): *m/z* = 266 [M^+].

2-Phenylimino-3-methyl-5-methylene-1,3-selenazolidine (3b) IR (neat): 1620, 1586 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.09 (3H, s, CH_3), 4.25 (2H, t, *J* = 2.3 Hz, CH_2), 5.20 (1H, dd, *J* = 2.3, 4.0 Hz, =CH_2), 5.57 (1H, dd, *J* = 1.7, 4.0 Hz, $^3J(^{77}Se\text{-}^1H)$ = 23.5 Hz, =CH_2), 6.90-6.97 (2H, m, Ar), 7.02-7.10 (1H, m, Ar), 7.23-7.31 (2H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.7, 60.5, 109.7, 121.7, 123.5, 128.9, 136.4, 153.0, 155.5; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 415.6; MS (EI): *m/z* = 252 [M^+]; Anal. Calcd for $C_{11}H_{12}N_2Se$: C, 52.60; H, 4.82; N, 11.15. Found: C, 52.37; H, 4.77; N, 10.74.

2-(4-Chlorophenyl)imino-3-methyl-5-methylene-1,3-selenazolidine (3c) IR (neat): 1620, 1584 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.08 (3H, s, CH_3), 4.27 (2H, t, *J* = 2.3 Hz, CH_2), 5.22 (1H, dd, *J* = 2.3, 4.0 Hz, =CH_2), 5.59 (1H, dd, *J* = 1.7, 4.0 Hz, $^3J(^{77}Se\text{-}^1H)$ = 23.5 Hz, =CH_2), 6.85 (2H, d, *J* = 8.6 Hz, Ar), 7.22 (2H, d, *J* = 8.6 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.7, 60.5, 110.0, 123.1, 128.6, 129.0, 136.0, 151.6, 156.0; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 417.7; MS (EI): *m/z* = 286 [M^+]; Anal. Calcd for

$C_{11}H_{11}ClN_2Se$: C, 46.25; H, 3.88; N, 9.81. Found: C, 46.34; H, 3.90; N, 9.42.

2-(2-Naphthyl)imino-3-methyl-5-methylene-1,3-selenazolidine (3d) mp 66.3-66.6 °C; IR (KBr): 1614, 1586 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.13 (3H, s, CH_3), 4.25 (2H, t, *J* = 2.3 Hz, CH_2), 5.18 (1H, dd, *J* = 2.3, 4.0 Hz, =CH_2), 5.56 (1H, dd, *J* = 1.7, 4.0 Hz, $^3J(^{77}Se\text{-}^1H)$ = 24.1 Hz, =CH_2), 7.15 (1H, dd, *J* = 1.7, 8.6 Hz, Ar), 7.30 (1H, s, Ar), 7.35 (1H, t, *J* = 6.9 Hz, Ar), 7.41 (1H, t, *J* = 6.9 Hz, Ar), 7.71-7.81 (3H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.8, 60.5, 109.8, 117.1, 123.2, 124.3, 125.9, 127.2, 127.6, 128.7, 130.6, 134.2, 136.4, 151.0, 155.8; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 419.6; MS (EI): *m/z* = 302 [M^+]; Anal. Calcd for $C_{15}H_{14}N_2Se$: C, 59.81; H, 4.68; N, 9.30. Found: C, 60.01; H, 5.00; N, 9.10.

2-Benzylimino-3-methyl-5-methylene-1,3-selenazolidine (3e) IR (neat): 1627, 1585 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.94 (3H, s, CH_3), 4.07 (2H, t, *J* = 2.3 Hz, CH_2), 4.26 (2H, s, CH_2), 5.19 (1H, dd, *J* = 2.3, 4.0 Hz, =CH_2), 5.52 (1H, dd, *J* = 1.7, 4.0 Hz, $^3J(^{77}Se\text{-}^1H)$ = 24.5 Hz, =CH_2), 7.10-7.28 (5H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.9, 60.3, 62.1, 109.9, 126.6, 127.4, 128.2, 136.4, 140.6, 155.6; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 403.6; MS (EI): *m/z* = 266 [M^+]; HRMS: *m/z* =267.0322, calcd. for $C_{12}H_{15}N_2Se$, found 267.0409 [M^++H].

2-Cyclohexylimino-3-methyl-5-methylene-1,3-selenazolidine (3f) IR (neat): 1645, 1587 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.12-1.48 (5H, m, ringCH_2), 1.54-1.65 (1H, m, ringCH_2), 1.70-1.82 (4H, m, ringCH_2), 2.35-2.46 (1H, m, ringCH_2), 2.93 (3H, s, CH_3), 4.06 (2H, t, *J* = 2.3 Hz, CH_2), 5.26 (1H, dd, *J* = 2.3, 4.0 Hz, =CH_2), 5.59 (1H, dd, *J* = 1.7, 4.0 Hz, $^3J(^{77}Se\text{-}^1H)$ = 22.3 Hz, =CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.0, 25.7, 34.1, 34.8, 60.0, 69.1, 109.5, 137.0, 151.7; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 392.1; MS (EI): *m/z* = 272 [M^+].

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