

# A Facile Synthesis of 2-Amino-1,3-selenazole by Reaction of *N,N*-Unsubstituted Selenourea with Ketone

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**ABSTRACT:** *2-Dialkylamino-1,3-selenazoles were yielded by the reaction of *N,N*-unsubstituted selenoureas with ketones in the presence of ferric chloride.* © 2006 Wiley Periodicals, Inc. *Heteroatom Chem* 17:88–92, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20180

## INTRODUCTION

There are many selenium-containing heterocyclic compounds found in the literature [1]. Of these many are potential pharmaceutical and dye agents [2]. The use of selenourea as the precursor is one of the most efficient methods for the synthesis of heterocyclic compounds containing selenium [3]. Recently, 2-dialkylamino-1,3-selenazole has become of interest as a starting material for preparing dyes. They are prepared according to the well-known method [4] from selenoureas and have been converted successfully into corresponding azo dye and squarylium dyes [5]. This result stimulates us to prepare these compound derivatives. We describe here the syntheses

of 2-dialkylamino-1,3-selenazoles by the reaction of selenoureas with ketones. This method would provide a new route to selenazoles without the use of lachrymatory halo carbonyl compounds.

## RESULTS AND DISCUSSION

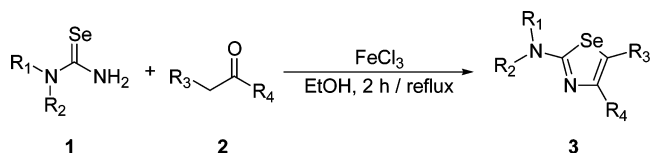
Various reactions were investigated to establish optimal conditions for the synthesis of 4-methyl-2-piperidino-1,3-selenazoles **3f**. The reaction of 1-selenocarbamoylpiperidine **1e** with acetone **2b** was carried out under an argon atmosphere. When reaction was carried out at reflux with acid or base such as BF<sub>3</sub>·Et<sub>2</sub>O, HCl, acetic acid, triethylamine, or di-isopropylethylamine, unidentifiable mixtures resulted. The reaction with ferric chloride yielded **3f** after a shorter time in higher yield. Next, the optimal solvent was investigated in the presence of ferric chloride. When ethanol, dichloromethane, and THF were used as a reaction solvent, the reaction using ethanol gave **3f** exclusively after a shorter time in high yields.

Using the optimal reaction conditions, several 2-amino-1,3-selenazoles **3a–l** were prepared from the reaction of corresponding *N,N*-unsubstituted selenoureas **1** with ketones **2** in the presence of ferric chloride (Scheme 1). The reaction gave **3** in moderate to high yields in the present study (Table 1). The reactions using aromatic ketone (**3h** in 32% yield)

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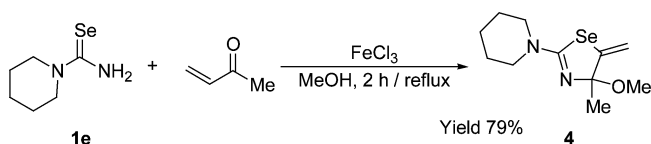


SCHEME 1

and ketones-bearing bulky groups (in the case of tertiary butyl group, 5% yield, data not shown) all gave **3** in low yields. The existence of ferrous chloride,  $\text{FeCl}_2$ , in the reaction mixture was confirmed by the addition of potassium ferricyanide. The  $^1J$  ( $^{77}\text{Se}$ – $^{13}\text{C}$ ) values (in the case of **3f**,  $J = 93.6$  Hz) at the C5 carbon and the  $^2J$  ( $^{77}\text{Se}$ – $^1\text{H}$ ) values (in the case of **3f**,  $J = 52.1$  Hz) at the C5 proton of **3** were clearly observed on the proton-decoupled  $^{13}\text{C}$  NMR and  $^1\text{H}$  NMR spectra. Although in the case of **3f** the isomeric 5-methyl-1,3-selenazole is a possible product, the possibility of its formation was ruled out by the observation of the  $^2J$  ( $^{77}\text{Se}$ – $^1\text{H}$ ) values and  $^1J$  ( $^{77}\text{Se}$ – $^{13}\text{C}$ ) values at the C5 carbon of **3**.

In order to elucidate the reaction mechanism for the formation of compound **3**, the reaction of selenourea, 1-selenocarbamoylpiperidine **1e**, with methyl vinyl ketone in methanol was attempted under similar conditions. This reaction afforded 4-methoxy-4-methyl-5-methylene-2-piperidino-4,5-dihydro-1,3-selenazole **4** in 79% yield (Scheme 2). In the case of compound **4**, elimination of alcohol from the selenazole ring could not proceed due to the lack of a proton at the C5 carbon. The formation of **4** was initiated by the nucleophilic addition of the nitrogen atom of selenourea **1** on the carbonyl carbon, affording the 4-methoxy-4,5-dihydro-1,3-selenazole **4**.

The formation of **3** could be explained by the following mechanism: the reaction of *N,N*-unsubstituted selenourea **1** with ketone **2** is initiated by the nucleophilic addition of the nitrogen of the selenourea to the carbonyl carbon, affording 2-amino-1,3-selenazole **3** (Scheme 3). Previously, it was reported that the reaction of *N,N*-unsubstituted selenoureas with  $\alpha$ -halocarboxylic acid led to the formation of 2-amino-1,3-selenazol-4-ones under reflux conditions [6], and 2-amino-



SCHEME 2

1,3-selenazole was prepared by allowing the ketone to react with iodine (or hypervalent iodine) and selenourea ( $\text{H}_2\text{N}-\text{C}(=\text{Se})-\text{NH}_2$ ) [7]. In the present study, it was confirmed that reacting *N,N*-unsubstituted selenourea **1** with ketone **2** in the presence of ferric chloride gives easily the corresponding 2-dialkylamino-1,3-selenazole **3**.

## EXPERIMENTAL

### General

Selenoureas were synthesized according to previously described procedures [8]. The  $^{77}\text{Se}$  chemical shifts are expressed in ppm deshielded with respect to near  $\text{Me}_2\text{Se}$  in  $\text{CDCl}_3$ .  $^2J$  ( $^{77}\text{Se}$ – $^1\text{H}$ ) values and  $^1J$  ( $^{77}\text{Se}$ – $^{13}\text{C}$ ) values are of the  $^{77}\text{Se}$  satellites of the  $^1\text{H}$  NMR spectra and proton-decoupled  $^{13}\text{C}$  NMR spectra.

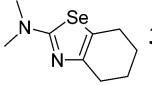
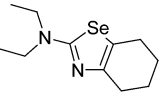
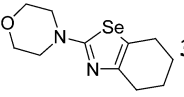
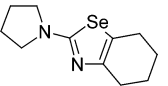
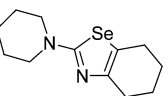
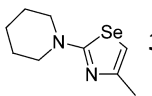
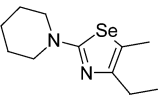
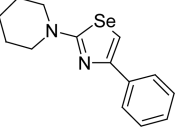
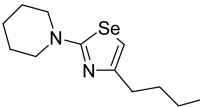
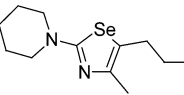
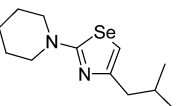
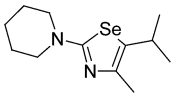
### General Procedure for Synthesis of 2-Dimethylamino-4,5,6,7-tetrahydrobenzo-1,3-selenazole **3a**

Cyclohexanone **2a** (0.10 mL, 0.9 mmol) was added to a stirred solution of *N,N*-dimethylselenourea **1a** (45 mg, 0.3 mmol) in dry ethanol (3 mL) under an argon atmosphere. Ferric chloride (0.19 g, 1.2 mmol) was added into the reaction mixture. The reaction mixture was refluxed for 2 h. The mixture was extracted with diethyl ether and washed with  $\text{H}_2\text{O}$ . The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with dichloromethane: *n*-hexane (2:1) to give **3a** (70 mg, quantitative) as yellow liquid. IR (neat): 2928, 1558  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.75–1.83 (4H, m,  $\text{CH}_2$ ), 2.56–2.59 (2H, m,  $\text{CH}_2$ ), 2.67–2.69 (2H, m,  $\text{CH}_2$ ), 3.04 (6H, s,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  23.1, 23.9, 25.4, 27.9, 41.0, 121.1, 147.1, 170.5;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ )  $\delta$  554.2; MS (FAB):  $m/z = 230$  [ $\text{M}^+$ ].

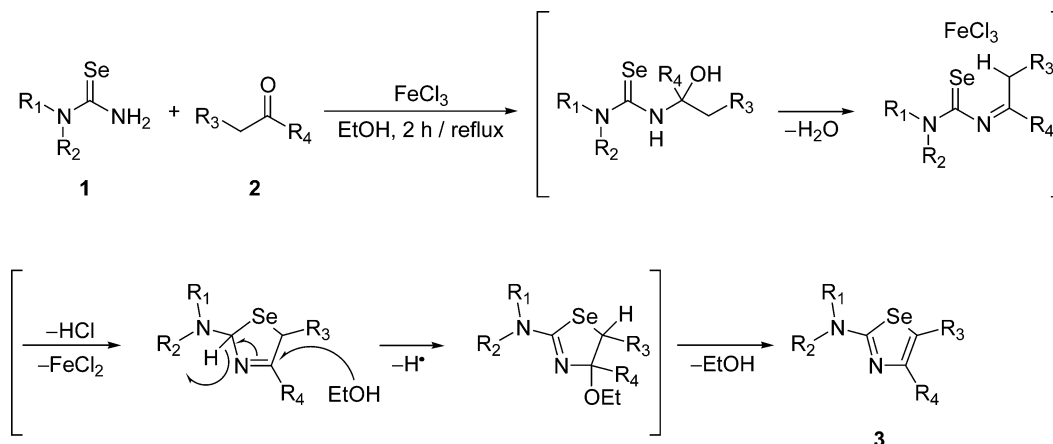
### 2-Diethylamino-4,5,6,7-tetrahydrobenzo-1,3-selenazole **3b**

Yellow liquid. IR (neat): 2930, 1544  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.21 (6H, t,  $J = 7.2$  Hz,  $\text{CH}_3$ ), 1.76–1.81 (4H, m,  $\text{CH}_2$ ), 2.54–2.57 (2H, m,  $\text{CH}_2$ ), 2.65–2.68 (2H, m,  $\text{CH}_2$ ), 3.42 (4H, q,  $J = 7.2$  Hz,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.7, 23.2, 23.9, 25.4, 27.9, 46.0, 119.7, 146.9, 168.7;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ ):  $\delta$  550.5; MS (CI):  $m/z = 259$  [ $\text{M}^+ + 1$ ].

TABLE 1 Synthesis of 2-Amino-1,3-selenazoles 3

| Selenourea 1                                                                                | Ketone 2                                                                                      | 2-Amino-1,3-selenazole 3                                                                       |                        |
|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------|
|                                                                                             |                                                                                               | Product                                                                                        | Yield (%) <sup>a</sup> |
|  <b>1a</b> |  <b>2a</b>   |  <b>3a</b>   | Quant.                 |
|  <b>1b</b> | <b>2a</b>                                                                                     |  <b>3b</b>   | 87                     |
|  <b>1c</b> | <b>2a</b>                                                                                     |  <b>3c</b>   | 83                     |
|  <b>1d</b> | <b>2a</b>                                                                                     |  <b>3d</b>   | Quant.                 |
|  <b>1e</b> | <b>2a</b>                                                                                     |  <b>3e</b>   | 97                     |
| <b>1e</b>                                                                                   |  <b>2b</b>  |  <b>3f</b>  | 85                     |
| <b>1e</b>                                                                                   |  <b>2c</b> |  <b>3g</b> | 73                     |
| <b>1e</b>                                                                                   |  <b>2d</b> |  <b>3h</b> | 32                     |
| <b>1e</b>                                                                                   |  <b>2e</b> |  <b>3i</b> | 20                     |
|                                                                                             |                                                                                               |  <b>3j</b> | 52                     |
| <b>1e</b>                                                                                   |  <b>2f</b> |  <b>3k</b> | 45                     |
|                                                                                             |                                                                                               |  <b>3l</b> | 19                     |

<sup>a</sup>Isolated yield. Reaction conditions: ketone **2** (3 equiv.), selenourea **1** (1 equiv.), dry ethanol, ferric chloride (4 equiv.), reflux, 2 h.



SCHEME 3

**2-Morpholino-4,5,6,7-tetrahydrobenzo-1,3-selenazole 3c**

Pink solid. mp: 52.0–54.0°C; IR (KBr): 2922, 2857, 1547  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.77–1.83 (4H, m,  $\text{CH}_2$ ), 2.55–2.58 (2H, m,  $\text{CH}_2$ ), 2.68–2.70 (2H, m,  $\text{CH}_2$ ), 3.38 (4H, t,  $J = 4.9$  Hz,  $\text{CH}_2$ ), 3.77 (4H, t,  $J = 4.9$  Hz,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  23.0, 23.8, 25.4, 27.8, 49.5, 66.2, 122.4, 146.8, 171.5;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ ):  $\delta$  562.5; MS (CI):  $m/z = 273$  [ $\text{M}^+ + 1$ ].

**2-Pyrrolidino-4,5,6,7-tetrahydrobenzo-1,3-selenazole 3d**

Yellow solid. mp 75.0–78.5°C; IR (KBr): 2924, 1540  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.76–1.83 (4H, m,  $\text{CH}_2$ ), 1.98–2.03 (4H, m,  $\text{CH}_2$ ), 2.58–2.60 (2H, m,  $\text{CH}_2$ ), 2.67–2.70 (2H, m,  $\text{CH}_2$ ), 3.38–3.41 (4H, m,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  23.1, 23.9, 25.46, 25.51, 27.9, 50.1, 120.1, 147.0, 166.7;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ ):  $\delta$  551.1; MS (CI):  $m/z = 257$  [ $\text{M}^+ + 1$ ].

**2-Piperidino-4,5,6,7-tetrahydrobenzo-1,3-selenazole 3e**

Yellow liquid. IR (neat): 2931, 2939, 1535  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.63–1.66 (6H, m,  $\text{CH}_2$ ), 1.75–1.82 (4H, m,  $\text{CH}_2$ ), 2.53–2.57 (2H, m,  $\text{CH}_2$ ), 2.66–2.68 (2H, m,  $\text{CH}_2$ ), 3.34–3.39 (4H, m,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  23.1, 23.8, 24.2, 25.1, 25.4, 27.8, 50.5, 120.9, 146.6, 171.1;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ ):  $\delta$  556.7; MS (CI):  $m/z = 271$  [ $\text{M}^+ + 1$ ].

**4-Methyl-2-piperidino-1,3-selenazole 3f [4]**

Yellow liquid. IR (neat): 2936, 2853, 1534  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.64–1.68 (6H, m,  $\text{CH}_2$ ),

2.21 (3H, s,  $\text{CH}_3$ ), 3.40–3.42 (4H, m,  $\text{CH}_2$ ), 6.56 (1H, s, CH) ( $^2J$  ( $^{77}\text{Se}-^1\text{H}$ ) = 52.1 Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  18.7, 24.2, 25.2, 50.7, 103.9, 150.2 ( $^1J$  ( $^{77}\text{Se}-^{13}\text{C}$ ) = 93.6 Hz), 173.5;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ ):  $\delta$  549.4; MS (CI):  $m/z = 231$  [ $\text{M}^+ + 1$ ].

**4-Ethyl-5-methyl-2-piperidino-1,3-selenazole 3g**

Yellow liquid. IR (neat): 2935, 2855, 1540  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.16 (3H, t,  $J = 7.7$  Hz,  $\text{CH}_3$ ), 1.59–1.67 (6H, m,  $\text{CH}_2$ ), 2.28 (3H, s,  $\text{CH}_3$ ), 2.44 (2H, q,  $J = 7.7$  Hz,  $\text{CH}_2$ ), 3.32–3.37 (4H, m,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.9, 13.9, 22.6, 24.3, 25.2, 50.5, 117.9, 150.5, 170.2;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ ):  $\delta$  580.6; MS (CI):  $m/z = 259$  [ $\text{M}^+ + 1$ ].

**4-Phenyl-2-piperidino-1,3-selenazole 3h [4]**

Yellow liquid. IR (neat): 2935, 2847, 1543  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.63–1.71 (6H, m,  $\text{CH}_2$ ), 3.51 (4H, t,  $J = 5.2$  Hz,  $\text{CH}_2$ ), 7.25 (1H, t,  $J = 7.5$  Hz, CH), 7.28 (1H, s, CH), 7.34 (2H, dd,  $J = 7.5$ , 8.3 Hz, CH), 7.85 (2H, d,  $J = 8.3$  Hz, CH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.3, 25.3, 50.8, 104.9 ( $^1J$  ( $^{77}\text{Se}-^{13}\text{C}$ ) = 97.2 Hz), 126.3, 127.2, 128.4, 136.1, 152.8, 172.8;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ ):  $\delta$  575.9; MS (CI):  $m/z = 293$  [ $\text{M}^+ + 1$ ].

**4-Butyl-2-piperidino-1,3-selenazole 3i**

Orange liquid. IR (neat): 2934, 2856, 1534  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.92 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_3$ ), 1.33–1.39 (2H, m,  $\text{CH}_2$ ), 1.59–1.66 (10H, m,  $\text{CH}_2$ ), 2.52 (2H, t,  $J = 7.5$  Hz,  $\text{CH}_2$ ), 3.40–3.43 (4H, m,  $\text{CH}_2$ ), 6.57 (1H, s, CH) ( $^2J$  ( $^{77}\text{Se}-^1\text{H}$ ) = 52.1 Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.0, 22.5, 24.3, 25.3, 30.8, 32.9, 50.7, 103.1, 155.4, 173.5;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ ):  $\delta$  544.4; MS (CI):  $m/z = 273$  [ $\text{M}^+ + 1$ ].

**4-Methyl-2-piperidino-5-propyl-1,3-selenazole 3j**

Orange liquid. IR (neat): 2933, 2855, 1535  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.95 (3H, t,  $J = 7.5$  Hz,  $\text{CH}_3$ ), 1.54–1.68 (8H, m,  $\text{CH}_2$ ), 2.10 (3H, s,  $\text{CH}_3$ ), 2.59 (2H, t,  $J = 7.5$  Hz,  $\text{CH}_2$ ), 3.34–3.36 (4H, m,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.5, 15.5, 24.2, 25.2, 26.0, 30.4, 50.4, 125.3 ( $^1J$  ( $^{77}\text{Se}$ – $^{13}\text{C}$ ) = 92.4 Hz), 143.9, 170.2;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ ):  $\delta$  561.5; MS (CI):  $m/z = 273$  [ $\text{M}^+ + 1$ ].

**4-(2-Methylpropyl)-2-piperidino-1,3-selenazole 3k**

Orange liquid. IR (neat): 2937, 2864, 1534  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.91 (6H, d,  $J = 6.9$  Hz,  $\text{CH}_3$ ), 1.62–1.67 (6H, m,  $\text{CH}_2$ ), 1.96–2.07 (1H, m, CH), 2.36 (2H, d,  $J = 7.5$  Hz,  $\text{CH}_2$ ), 3.39–3.41 (4H, m,  $\text{CH}_2$ ), 6.56 (1H, s, CH) ( $^2J$  ( $^{77}\text{Se}$ – $^1\text{H}$ ) = 52.1 Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  22.5, 24.3, 25.2, 27.7, 42.5, 50.7, 104.3 ( $^1J$  ( $^{77}\text{Se}$ – $^{13}\text{C}$ ) = 93.6 Hz), 154.3, 173.4;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ ):  $\delta$  542.6; MS (CI):  $m/z = 273$  [ $\text{M}^+ + 1$ ].

**4-Methyl-5-(2-methylethyl)-2-piperidino-1,3-selenazole 3l**

Yellow solid. mp: 38.0–40.0°C; IR (KBr): 2934, 2853, 1541  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.20 (6H, d,  $J = 6.9$  Hz,  $\text{CH}_3$ ), 1.59–1.67 (6H, m,  $\text{CH}_2$ ), 2.12 (3H, s,  $\text{CH}_3$ ), 3.00–3.07 (1H, m,  $J = 6.9$  Hz, CH), 3.37 (4H, t,  $J = 5.2$  Hz  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  15.7, 24.3, 25.3, 26.1, 29.2, 50.4, 134.3, 142.0, 170.0;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ ):  $\delta$  528.9; MS (CI):  $m/z = 273$  [ $\text{M}^+ + 1$ ].

**4-Methoxy-4-methyl-5-methylene-2-piperidino-4,5-dihydro-1,3-selenazole 4**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.60–1.68 (6H, m,  $\text{CH}_2$ ), 2.17 (3H, s,  $\text{CH}_3$ ), 3.33 (3H, s,  $\text{CH}_3$ ), 3.38–3.43 (4H, m,  $\text{CH}_2$ ), 3.00–3.07 (1H, m,  $J = 6.9$  Hz, CH), 4.46 (2H, s,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  15.7, 24.1, 25.1, 50.4, 56.9, 67.9, 120.22 ( $^1J$  ( $^{77}\text{Se}$ – $^{13}\text{C}$ ) = 91.2 Hz), 147.6, 171.9;  $^{77}\text{Se}$  NMR (95 MHz,  $\text{CDCl}_3$ ):  $\delta$  564.5; MS (CI):  $m/z = 274$  [ $\text{M}^+ + 1$ ].

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