A Facile Preparation of Selenohydantoins Using Isoselenocyanate

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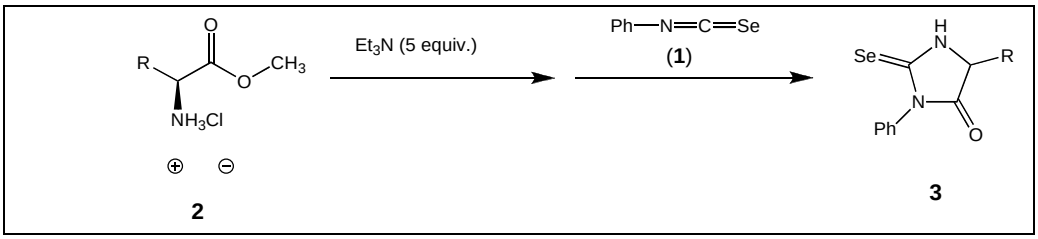

Reactions of isoselenocyanate with methyl aminoacetate hydrochlorides in the presence of triethylamine afforded selenohydantoins, 2-selenoxoimidazolidin-4-ones, in high yields.

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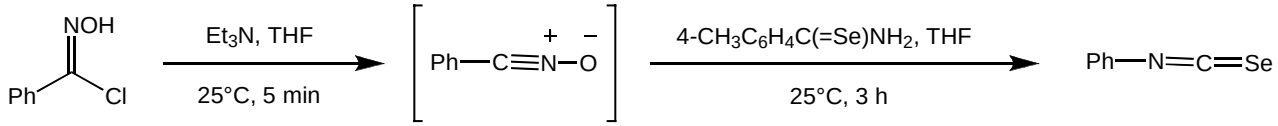
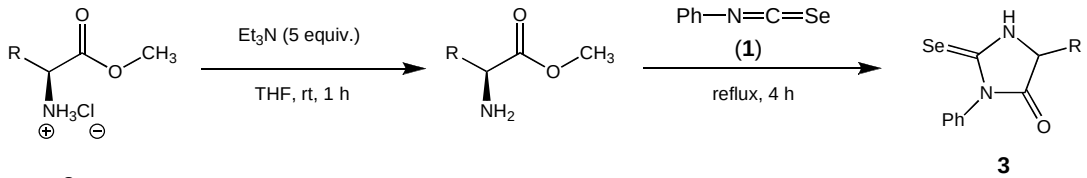
Hydantoins represent an important class of biologically active molecules such as anticancer, antimuscarinic, anticovulsant, antiulcer, [1] herbicide and fungicide. [2] Numerous hydantoin syntheses have been reported in the literature [3]. Extensive studies of the chemistry [4] and biology [5] of thiohydantoin derivatives have also been established. In contrast, the reports of selenohydantoin have been limited [6]. Devillanova *et al*. have studied crystal structure, calculation and spectral analysis of 5,5-dimethylimidazolidine-2,4-dichalcogen derivatives including 5,5-dimethyl-2-selenoxoimidazolidin-4-one. [7] We describe here the syntheses of 5-alkyl-2-selenoxo-imidazolidin-4-ones, selenohydantoins derivatives, using isoselenocyanate.

Phenyl isoselenocyanate **1** has been prepared by a previous method [8]. Previously we failed to isolate compound **1**. When acidic silica gel was used, compound **1** decomposed, however, compound **1** could be isolated by using neutral silica gel (Scheme 1). Compound **1**, obtained as described above, was used for synthesis of selenohydantoins. Into the reaction mixture of methyl L-alanine methyl ester hydrochloride **2a** with triethylamine (5 equiv.), phenyl isoselenocyanate **1** was added and stirred at room temperature for 4 h. Usual workup led to 5-methyl-3-phenyl-2-selenoxoimidazolidin-4-one **3a** in 80% yield. The structure of **3a** was elucidated by studies of IR, ^{1}H-, ^{13}C-, ^{77}Se-NMR, COSY, HMQC data, MS, and elemental analysis. IR [7j] and ^{1}H-, ^{13}C-NMR [9] data of compound **3** are consisted with previously reported data of seleno- and thiohydantoins. Chemical shifts of compound **3** in ^{77}Se-NMR were observed at δ 268±16 which are typical ^{77}Se NMR chemical shifts of seleno-

Scheme 1



Scheme 2

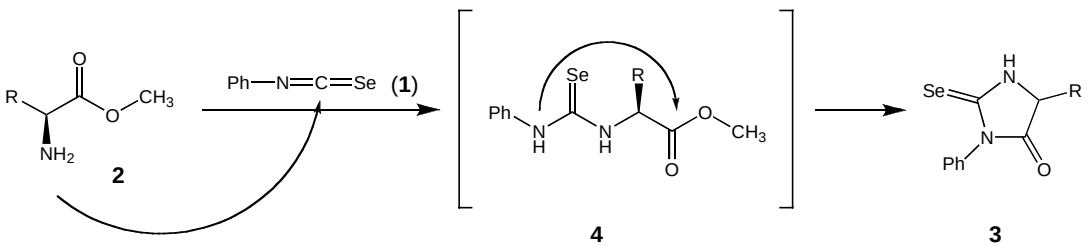


R	Yield (%)
CH_3-	**3a**: 80
$(CH_3)_2CH$-	**3b**: 97
$CH_3S(CH_2)_2$-	**3c**: quant.
$C_6H_5CH_2$-	**3d**: 76
H-	**3e**: 28

ureas [10]. The retention or loss of stereochemical integrity in the products is presently unknown. In this reaction, 5 equiv. triethylamine of was essential for elimination of hydrochloride. Under the optimal reaction conditions, five kinds of 5-alkyl-2-selenoxoimidazolidin-4-ones **3** were prepared by reactions of phenyl isoselenocyanate **1** with methyl aminoacetate hydrochlorides **2** in the presence of triethylamine (Scheme 2).

5-Alkyl-3-phenyl-2-selenoxoimidazolidin-4-ones **3** were obtained in high yields except 3-phenyl-2-selenoxoimidazolidin-4-one **3e**. In the case of reaction with **2e**, *N*-phenyl-*N*'-[(methoxycarbonyl)methyl]selenourea **4** was obtained in 50% yield. The treatment of compound **4** with Et_3N afforded **3e**. The selenourea **4** is thought to be an intermediate to form the imidazolidin-4-ones **3**. From the results, the formation of 5-alkyl-3-phenyl-2-selenoxoimidazolidin-4-ones **3** could be explained by the mechanism described in Scheme 3. The formation of **3** is initiated on the nucleophilic addition of amino group of methyl aminoacetate to carbon of phenyl isoselenocyanate **1**, affording the selenourea derivative **4**. Then cyclization proceeded to give the 5-alkyl-2-selenoxoimidazolidin-4-ones **3**.

Scheme 3



Hence, selenohydantoin derivatives, 2-selenoxoimidazolidin-4-ones **3**, have been obtained by the reactions of isoselenocyanate **1** with methyl aminoacetate hydrochlorides **2** in the presence of triethylamine in high yields.

EXPERIMENTAL

General. The ^{77}Se nmr (95 MHz) spectra were obtained from a JEOL ECA500 spectrometer, and ^{77}Se chemical shifts are expressed in ppm deshielded with respect to Me_2Se in $CDCl_3$ or DMSO-*d6*. Neutral silica gel (Silica Gel 60N, spherical, neutral, 40-50 μm) was purchased from Kanto Chemical Co., Inc. (Tokyo, Japan).

Synthesis of Phenyl Isoselenocyanate (**1**) [11]. To THF solution (40 mL) of phenyl hydroximoyl chloride (0.77 g, 5 mmol), triethylamine (0.68 mL, 1.0 equiv.) was added and stirred at 25°C for 5 min. Then 4-tolylselenoamide (1.0 g, 10 mmol) was added to the reaction mixture and stirred at same temperature for 3 hours. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography on neutral silica gel using *n*-hexane: dichloromethane (1:1) as eluent to give **1** (0.21 g, 23%); Yellow oil; ir (neat): 2116, 749 cm^{-1}. ^{1}H nmr (500 MHz, deuteriochloroform): δ 7.22-7.40 (5H, m, Ar), ^{13}C nmr (125 MHz, deuteriochloroform): δ 126.2, 128.2, 129.7, 129.8 (Ar), ^{77}Se nmr (95 MHz, deuteriochloroform): δ -295.9, ms (CI): *m/z* = 184 [M$^+$+1].

General Procedure for Synthesis of 5-Methyl-3-phenyl-2-selenoxoimidazolidin-4-one (**3a**). Triethylamine (0.7 mL, 5.0 mmol) was added to a stirred THF solution (15 mL) of L-alanine methyl ester hydrochloride **2a** (0.14 g, 1.0 mmol). The reaction mixture was stirred at room temperature for 1 hour. Then, to the reaction mixture, phenyl isoselenocyanate **1** (0.18 g, 1 mmol) was added and the mixture was refluxed for 4 hours. The mixture was extracted with dichloromethane, washed with aqueous 1% $NaHSO_4$ and water. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with dichloromethane as the eluent to give **3a** (0.2 g, 80%) as white solid; mp 165-167 °C, ir (potassium bromide): 3159, 1758, 1521 cm^{-1}. ^{1}H nmr (500 MHz, DMSO-*d6*): δ 1.41 (3H, d, *J* = 6.9 Hz, CH_3), 4.33 (1H, q, *J* = 6.9 Hz, CH), 7.31 (2H, d, *J* = 7.5 Hz, Ar), 7.43-7.50 (3H, m, Ar), 11.2 (1H, br, NH), ^{13}C nmr (125 MHz, DMSO-*d6*): δ 16.1, 56.9, 129.2, 129.3, 129.6, 134.7, 175.2, 182.6, ^{77}Se nmr (95 MHz, DMSO-*d6*): δ 256.4, ms (CI): *m/z* = 255 [M$^+$+1]. *Anal*. Calcd. for $C_{10}H_9N_2OSe$: C, 47.63; H, 3.60; N, 11.11. Found: C, 47.42; H, 3.77; N, 12.22.

5-Isopropyl-3-phenyl-2-selenoxoimidazolidin-4-one (**3b**). White crystals; mp 181-184 °C, ir (potassium bromide): 3162, 1757, 1513 cm^{-1}. ^{1}H nmr (500 MHz, DMSO-*d6*): δ 0.93 (3H, d, *J* = 6.9 Hz, CH_3), 1.06 (3H, d, *J* = 6.9 Hz, CH_3), 2.20 (1H, m, CH), 4.22 (1H, d, *J* = 3.4 Hz, CH), 7.25 (2H, d, *J* = 7.5 Hz, Ar), 7.42-7.51 (3H, m, Ar), 11.3 (1H, br, NH), ^{13}C nmr (125 MHz, DMSO-*d6*): δ 16.8, 18.7, 30.8, 66.2, 129.3, 129.5, 134.6, 174.0, 183.4, ^{77}Se nmr (95 MHz, DMSO-*d6*): δ 257.0, ms (CI): *m/z* = 283 [M$^+$+1]. *Anal*. Calcd. for $C_{12}H_{13}N_2OSe$: C, 51.44; H, 4.68; N, 10.00. Found: C, 51.31; H, 4.72; N, 10.16.

5-(3-Thiabutyl)-3-phenyl-2-selenoxoimidazolidin-4-one (**3c**). Pink crystals; mp 148-150 °C, ir (potassium bromide): 3158, 1761, 1512 cm^{-1}. ^{1}H nmr (500 MHz, deuteriochloroform): δ 2.10 (3H, s, CH_3), 2.18 (1H, m, CH_2), 2.33 (1H, m, CH_2), 2.71 (2H, t, *J* = 6.9 Hz, CH_2), 4.28 (1H, dd, *J* = 4.6, 6.9 Hz, CH), 7.33 (2H, m, Ar), 7.45-7.52 (3H, m, Ar), 9.19 (1H, br, NH), ^{13}C nmr (125 MHz, deuteriochloroform): δ 15.3, 29.6, 30.1, 60.0, 128.5, 129.3, 133.4, 173.1, 184.9, ^{77}Se nmr (95 MHz, deuteriochloroform): δ 284.7, ms (CI): *m/z* = 315 [M$^+$+1]. *Anal*. Calcd. for $C_{12}H_{13}N_2OSSe$: C, 46.16; H, 4.20; N, 8.97. Found: C, 46.14; H, 4.41; N, 9.13.

5-Benzyl-3-phenyl-2-selenoxoimidazolidin-4-one (**3d**). White crystals; mp 187-190 °C, ir (potassium bromide): 3130, 1755, 1513 cm^{-1}. ^{1}H nmr (500 MHz, DMSO-*d6*): δ 3.13 (1H, dd, *J* = 6.9, 14.0 Hz, CH_2), 3.30 (1H, dd, *J* = 4.0, 6.9 Hz, CH_2), 4.05 (1H, dd, *J* = 4.0, 14.0 Hz, CH), 6.00-7.01 (2H, m, Ar), 7.43-7.44

(3H, m, Ar), 9.00 (1H, br, NH), ^{13}C nmr (125 MHz, DMSO-*d*6): δ 36.9, 62.0, 127.9, 128.3, 129.1, 129.4, 129.5, 133.0, 133.6, 173.8, 183.6, ^{77}Se nmr (95 MHz, DMSO-*d*6): δ 286.2, ms (CI): *m*/*z* = 331 [M$^+$+1]. *Anal*. Calcd. for $C_{16}H_{13}N_2OSe$: C, 58.55; H, 3.99; N, 8.53. Found: C, 58.51; H, 4.18; N, 8.61.

3-Phenyl-2-selenoxoimidazolidin-4-one (3e). White crystals; mp 230 ºC, ir (potassium bromide): 3125, 1764, 1512 cm^{-1}. ^{1}H nmr (500 MHz, DMSO-*d*6): δ 4.18 (2H, s, CH_2), 7.28-7.51 (5H, m, Ar), 11.1 (1H, br, NH), ^{13}C nmr (125 MHz, DMSO-*d*6): δ 50.9, 129.2, 129.6, 134.7, 134.7, 172.5, 183.7, ^{77}Se nmr (95 MHz, DMSO-*d*6): δ 254.9, ms (CI): *m*/*z* = 241 [M$^+$+1]. *Anal*. Calcd. for $C_9H_7N_2OSe$: C, 45.40; H, 2.96; N, 11.76. Found: C, 45.57; H, 2.82; N, 11.51.

***N*-Phenyl-*N*'-[(methoxycarbonyl)methyl]selenourea (4).** Yellow oil, ir (nujol): 3368, 3150, 2986, 1538 cm^{-1}, ^{1}H nmr (500 MHz, $CDCl_3$): δ 3.75 (3H, s, CH_3), 4.51 (2H, d, *J* =4.6 Hz, CH_2), 6.98 (1H, br, NH), 7.27-7.35 (3H, m, Ar), 7.42-7.47 (2H, m, Ar), 9.09 (1H, br, NH), ^{13}C nmr (125 MHz, $CDCl_3$): δ 49.0, 52.5, 124.8, 127.6, 130.1, 135.6, 169.8, 178.8, ^{77}Se nmr (95 MHz, $CDCl_3$): δ 229.5, ms (CI): *m*/*z* = 273 [M$^+$+1]. *Anal*. Calcd. for $C_{10}H_{12}N_2O_2Se$: C, 44.29; H, 4.46; N, 10.33. Found: C, 44.14; H, 4.47; N, 10.34.

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