A Facile Preparation of 2-Amino-1,3-selenazoles by Reactions of *N*,*N*-Unsubstituted Selenoureas with Chloroacetonitrile

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Reactions of *N*,*N*-unsubstituted selenoureas **1** with chloroacetonitrile **2** was investigated. When anhydrous solvent was used, the reaction gave cyanomethyl 1-piperidinoselenocarboimidate hydrochloride **3**. The reaction in solvent including water yielded 2-amino-4,5-dihydro-1,3-selenazol-4-iminium chlorides **4** in moderate to high yields.

Syntheses of 1,3-selenazoles, which are selenium-containing 5-membered heterocycles, 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-selenazoles use selenoamide[3] or selenourea[4] as the starting material. Recently, it was reported that 1,3-selenazoles possess strong inhibitory activity against inducible nitric oxide synthase.[5] From the results of the investigation of structure–biological activity relationships, 1,3-selanazole skeleton bearing specific substituent groups has been indicated to influence strongly the activity. Therefore, the preparation of many kinds of 1,3-selenazole derivatives has been desired for the development of potential agents. Herein, we furthermore describe the syntheses of other kinds of 1,3-selenazoles using *N*,*N*-unsubstituted selenoureas.

N,*N*-Unsubstituted selenoureas **1** were prepared by a reaction of cyanamides with LiAlHSeH according to previous reports.[6] Next, we investigated reactions of the *N*,*N*-unsubstituted selenourea, 1-selenocarbamoylpiperidine **1d**, with chloroacetonitrile **2** in various solvents (Scheme 1, Table 1). Reaction in anhydrous solvent gave cyanomethyl 1-piperidinoselenocarboimidate hydrochloride **3** as a sole product (Table 1, Entries 1–3). Crystal structure of the selenouronium chloride **3** was determined by X-ray diffraction analysis (Figure 1).[7,8] Reaction in ethanolic solution containing 1% water gave only 2-piperidino-4,5-dihydro-1,3-selenazol-4-iminium chloride **4d** in 91% yield (Table 1, Entry 5).

Under the optimal reaction conditions for synthesis of the **4d** (Table 1, Entry 5), five kinds of 2-amino-4,5-dihydro-1,3-selenazol-4-iminium chlorides **4a**–**4e**[8] were prepared by reactions of *N*,*N*-unsubstituted selenoureas **1a**–**1e** with chloroacetonitrile **2** in ethanol containing 1% water as a solvent (Scheme 2).

The reaction mechanism for a formation of **4** can be explained by the route presented in Scheme 3. The selenouronium chlorides **3** were available by the nucleophilic addition of selenium of selenourea **1** to methylene carbon of nitrile **2**. Then via the compounds **3**, an annulation proceeded, affording **4** (Scheme 3).

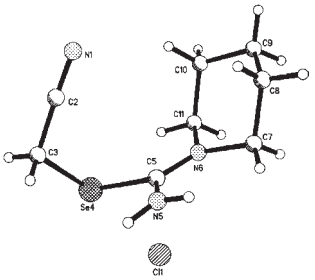
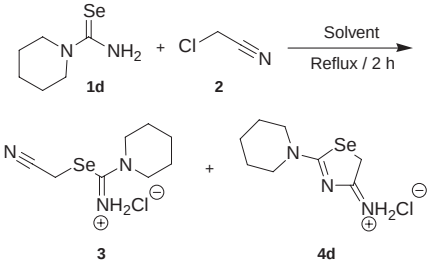


Figure 1. ORTEP diagram (50% thermal ellipsoids) of cyanomethyl 1-piperidinoselenocarboimidate hydrochloride **3**.

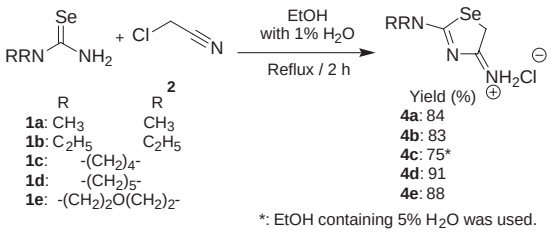
Table 1. Reaction of 1-selenocarbamoylpiperidine **1d** with chloroacetonitrile **2** in various solvents

Entry	Solvent	Yield/%	
		3[a]	**4d**[b]
1	Anhydrous THF	74	0
2	Anhydrous CH_2Cl_2	22	0
3	Anhydrous Acetone	59	0
4	Acetone with 10% H_2O	27	54
5	EtOH with 1% H_2O[c]	0	91
6	EtOH with 10% H_2O	0	78

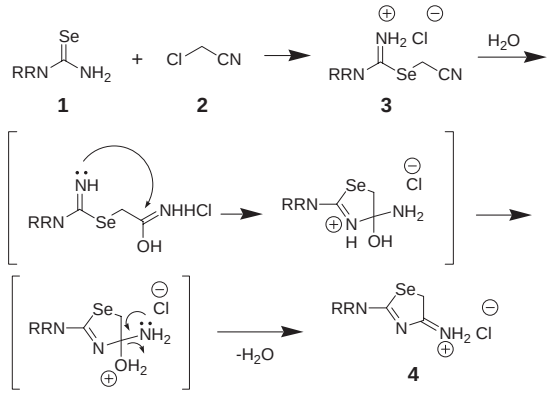
[a]**3**: Cyanomethyl 1-piperidinoselenocarboimidate hydrochloride. [b]**4d**: 2-Piperidino-1,3-selenazol-4-iminium chloride. [c]Reaction conditions: chloroacetonitrile **2** (33 μL, 0.5 mmol) was added to ethanol including 1% H_2O (10 mL) of 1-selenocarbamoylpiperidine **1d** (90 mg, 0.5 mmol). The reaction mixture was refluxed for 2 h.



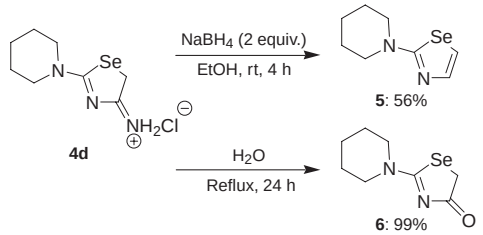
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

2-Piperidino-1,3-selenazole **5**[9] was afforded by the reaction of 2-piperidino-4,5-dihydro-1,3-selenazol-4-iminium chloride **4d** with sodium borohydride (2 equiv.) in 56% yield. A reaction of aqueous **4d** under reflux gave 2-piperidino-4,5-dihydro-1,3-selenazol-4-one **6**[10] in 99% yield (Scheme 4).

2-Amino-1,3-selenazol-4-iminium chloride was obtained by the reaction of selenourea [$H_2NC(=Se)NH_2$] with chloroacetonitrile previously.[11] Synthesis of *N*-substituted 1,3-selenazol-4-iminium chloride **4** using *N*,*N*-unsubstituted selenoureas **1** has hardly been reported.[9] In this letter, we confirmed the existence and structure of selenouronium chloride **3** by X-ray diffraction analysis, which is an intermediate of 2-amino-1,3-selenazol-4-iminium chloride, and described synthesis of 2-substituted 1,3-selenazol-4-iminium chloride.

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References and Notes

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7 CCDC No. 275354 for **3** contains the supplementary crystallographic data for this letter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

8 Spectral data of selected compounds. Cyanomethyl 1-piperidinoselenocarboimidate hydrochloride **3**: Colorless crystals, mp: 184.6–185.5 °C; ^{1}H NMR (500 MHz, DMSO): δ 1.65 (6H, m, $3 \times CH_2$), 3.80 (4H, m, $2 \times CH_2$), 4.43 (2H, s, CH_2, $^2J_{77Se\text{-}1H} = 16.6$ Hz), 9.89 (2H, s, $2 \times$ NH); ^{13}C NMR (125 MHz): δ 10.2, 23.0, 25.7, 117.9, 160.4; ^{77}Se NMR (95 MHz): δ 425.0; MS (CI): $m/z = 232$ ($M^+ + 1 -$ HCl); 2-Dimethylamino-4,5-dihydro-1,3-selenazol-4-iminium chloride **4a**: Yellow solid, mp: 157.3 °C; ^{1}H NMR (500 MHz, DMSO): δ 3.26 (3H, s, CH_3), 3.36 (3H, s, CH_3), 4.79 (2H, s, CH_2), 10.0 (1H, brs, NH), 10.2 (1H, brs, NH); ^{13}C NMR (125 MHz): δ 37.4, 41.0, 43.6, 182.2, 182.9; ^{77}Se NMR (95 MHz): δ 416.0; MS (CI): $m/z = 192$ ($M^+ + 1 -$ HCl); 2-Piperidino-4,5-dihydro-1,3-selenazol-4-iminium chloride **4d**: White solid, mp: 227.5 °C; ^{1}H NMR (500 MHz, DMSO): δ 1.59–1.71 (6H, m, $3 \times CH_2$), 3.52–3.58 (2H, m, CH_2), 3.95 (2H, t, $J = 5.4$ Hz, CH_2), 4.75 (2H, s, CH_2), 10.0 (1H, brs, NH), 10.2 (1H, brs, NH); ^{13}C NMR (125 MHz): δ 23.0, 25.3, 25.8, 36.5, 50.3, 54.7, 180.6, 182.7; ^{77}Se NMR (95 MHz): δ 414.7; MS (CI): $m/z = 232$ ($M^+ + 1 -$ HCl).

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