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SYNTHESIS OF 2-AMINO-1,3-SELENAZOLES BY REACTION OF *N*,*N*-UNSUBSTITUTED SELENOUREAS WITH α,β-UNSATURATED ALDEHYDES

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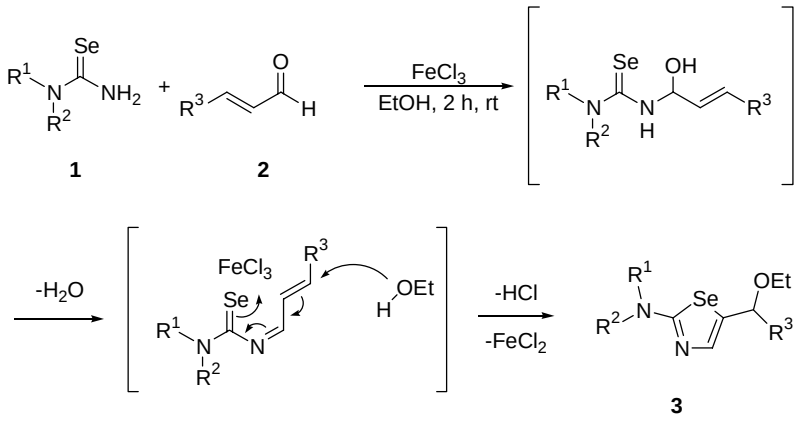
Abstract – 2-Dialkylamino-1,3-selenazoles were obtained by the reaction of *N*,*N*-unsubstituted selenoureas with α,β-unsaturated aldehydes in alcohol in the presence of ferric chloride at room temperature.

INTRODUCTION

There are many 1,3-selenazoles found in the literatures.[1] Many of them are studied as potential pharmaceutical and dye agents.[2] 1,3-Selenazole derivatives remarkably inhibited lipopolysaccharide-induced nitric oxide (NO) production in BV-2 cells. The 1,3-selenazole derivatives inhibited NO production dose-dependently without toxicity to BV-2 cells. From the investigation of structure-biological activity relationships, 1,3-selenazole skeleton bearing specific substituent groups has been indicated to influence strongly the activity.[3] Therefore, the preparation of many kinds of 2-amino-1,3-selenazoles has been desired for the development of potential agents. For the synthesis of 2-amino-1,3-selenazoles, the use of selenoureas is one of the most functional starting materials. For the synthesis of 2-amino-1,3-selenazole derivatives using selenoureas, several methods have been developed. For example, reactions of selenourea with α-haloketones,[4] chloroacetonitrile[5] and α-haloacyl halides[6] afforded the 2-amino-1,3-selenazole derivatives. Most of methods include the use of lachrymatory halocarbonyl compounds. Recently we have reported a new route to 2-amino-1,3-selenazoles by reactions of *N*,*N*-unsubstituted selenoureas with ketones in the presence of ferric chloride without use of lachrymatory halo carbonyl compounds.[7] In our continuous studies, we describe here the syntheses of

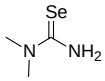
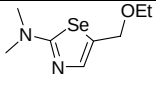
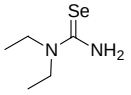
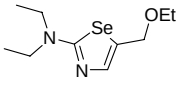
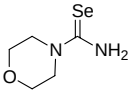
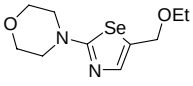
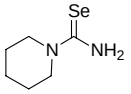
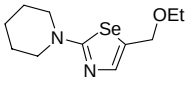
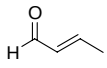
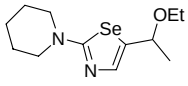
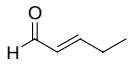
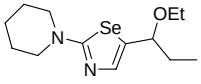
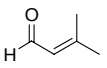
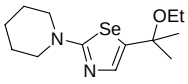
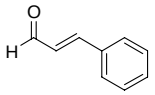
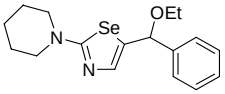
2-dialkylamino-1,3-selenazole derivatives by the reaction of *N*,*N*-unsubstituted selenoureas with α,β-unsaturated aldehydes in alcohol.

RESULTS AND DISCUSSION



Scheme 1

Table 1. Synthesis of 2-Amino-1,3-selenazoles (**3**)

Entry	Selenourea (**1**)	α,β-Unsaturated Aldehyde (**2**)	2-Amino-1,3-selenazole (**3**)	
			Product	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	68
2	 **1b**	**2a**	 **3b**	74
3	 **1c**	**2a**	 **3c**	63
4	 **1d**	**2a**	 **3d**	93
5	**1d**	 **2b**	 **3e**	49
6	**1d**	 **2c**	 **3f**	26
7	**1d**	 **2d**	 **3g**	18
8	**1d**	 **2e**	 **3h**	0

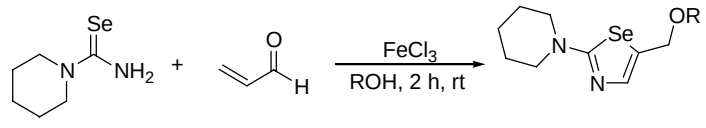
[a] Isolated yield.

Optimal conditions for the reaction of 1-selenocarbamoylpiperidine (**1d**) with 2-propenal (**2a**) were studied. The previously reported reactions of *N*,*N*-unsubstituted selenoureas with ketones in the presence

of ferric chloride were carried out under reflux conditions affording 2-amino-1,3-selnazoles in high yields.[7a] The reactions of **1d** with **2a** in the presence of ferric chloride under reflux conditions in ethanol gave unidentifiable mixtures, whilst the reaction at room temperature afforded 5-(ethoxymethyl)-2-piperidino-1,3-selenazole (**3d**) in 93% yield (Scheme 1). The structure of **3d** was elucidated by studies of IR, ^{1}H-, ^{13}C-, ^{77}Se-NMR and elemental analysis. Reactions of *N*,*N*-unsubstituted selenoureas (**1a-d**) with **2a** gave the corresponding 2-amino-5-(ethoxymethyl)-1,3-selenazole (**3a-d**) in 63-93% yields (Table 1, Entries 1-4). Using the optimal reaction conditions, several 2-amino-1,3-selenazole derivatives (**3a-g**) were prepared from the reactions of corresponding *N*,*N*-unsubstituted selenoureas (**1a-d**) with α,β-unsaturated aldehydes (**2a-d**) in the presence of ferric chloride (Table 1). The structures of products (**3a-g**) were determined by comparing the spectral data with those of **3d**. Reaction with cinnamaldehyde (**2e**) did not proceed (Table 1, Entry 8).

The formation of **3** could be thought to be the similar pathway of the products by reaction of *N*,*N*-unsubstituted selenourea (**1**) with α,β-unsaturated ketones.[7b] The reaction of **1** with α,β-unsaturated aldehydes (**2**) is initiated by the nucleophilic addition of the nitrogen of the selenourea to the carbonyl carbon, affording 2-amino-1,3-selenazoles (**3**) (Scheme 1).

Reactions in other alcohols were carried out. Reactions of **1d** with **2a** in methanol, isopropyl alcohol and *tert*-butyl alcohol also gave corresponding 5-(alkoxymethyl)-2-amino-1,3-selenazole derivatives (**4**) in 51-79% yields. Reaction in phenol gave only unidentifiable mixtures instead of **4**.



R	Yield (%)
CH_3	58 (**4a**)
$(CH_3)_2CH$	79 (**4b**)
$(CH_3)_3C$	51 (**4c**)

1d **2a** **4**

Scheme 2

In the present study, it was confirmed that the reactions of *N*,*N*-unsubstituted selenoureas (**1**) with α,β-unsaturated aldehydes (**2**) in alcohol in the presence of ferric chloride give several type of 2-dialkylamino-1,3-selenazole derivatives (**3**) at room temperature.

EXPERIMENTAL

General

Selenoureas were synthesized according to previously described procedures.[8] The ^{77}Se chemical shifts are expressed in ppm deshielded with respect to Me_2Se in $CDCl_3$. ^{3}J (^{77}Se-^{1}H) values and ^{1}J (^{77}Se-^{13}C) values are the ^{77}Se satellites of the ^{1}H NMR spectra and proton-decoupled ^{13}C NMR spectra, respectively.

General procedure for synthesis of 2-dimethylamino-5-ethoxymethyl-1,3-selenazole (3a). 2-Propenal (**2a**) (0.10 ml, 1.5 mmol) was added to a stirred solution of *N*,*N*-dimethylselenourea (**1a**) (70 mg, 0.5 mmol) in dry ethanol (5 mL) under an argon atmosphere. Ferric chloride (0.29 g, 1.8 mmol) was added into the reaction mixture. The reaction mixture was stirred for 2 h under room temperature. The mixture was diluted with ethyl acetate and saturated Na_2CO_3 aq. The organic layer was separated, dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with diethyl ether:hexane (1:3) to give **3a** (79.2 mg, 68 %) as yellow liquid. IR (neat): 2868, 1555 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.20 (3H, t, *J* =6.9 Hz, CH_3), 3.08 (6H, s, CH_3), 3.50 (2H, q, *J* =6.9 Hz, CH_2), 4.55 (2H, s, CH_2, ^3J (^{77}Se-^{1}H) = 9.7 Hz), 6.99 (1H, s, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.0, 40.9, 64.4, 67.1, 128.8, 139.6, 174.8; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 542.7; Anal. Calcd for $C_8H_{14}N_2OSe$: C, 41.21; H, 6.05; N, 12.01. Found: C, 41.44; H, 5.86; N, 11.78.

2-Diethylamino-5-ethoxymethyl-1,3-selenazole (3b) Orange liquid. IR (neat): 2973, 1539 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.21 (3H, t, *J* =6.9 Hz, CH_3), 1.23 (6H, t, *J* =6.9 Hz, CH_3), 3.45 (4H, q, *J* =6.9 Hz, CH_2), 3.51 (2H, q, *J* =6.9 Hz, CH_2), 4.55 (2H, s, CH_2, ^3J (^{77}Se-^{1}H) = 9.7 Hz), 6.95 (1H, s, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.5, 15.0, 46.4, 64.4, 67.1, 127.2, 139.4, 173.1; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 538.9; Anal. Calcd for $C_{10}H_{18}N_2OSe$: C, 45.98; H, 6.95; N, 10.72. Found: C, 46.04; H, 7.23; N, 10.50.

5-Ethoxymethyl-2-morpholino-1,3-selenazole (3c) Yellow solid. mp 58–59 °C; IR (KBr): 2860, 1543 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.13 (3H, t, *J* =6.9 Hz, CH_3), 3.37 (4H, t, *J* =5.2 Hz, CH_2), 3.43 (2H, q, *J* =6.9 Hz, CH_2), 3.72 (4H, t, *J* =5.2 Hz, CH_2), 4.49 (2H, s, CH_2, ^3J (^{77}Se-^{1}H) = 9.7 Hz), 6.93 (1H, s, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.1, 49.4, 64.6, 66.1, 67.0, 130.3, 139.0, 175.7; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 553.5; Anal. Calcd for $C_{10}H_{16}N_2O_2Se$: C, 43.64; H, 5.86; N, 10.18. Found: C, 43.44; H, 6.09; N, 10.39.

5-Ethoxymethyl-2-piperidino-1,3-selenazole (3d) Yellow liquid. IR (neat): 2935, 1527 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.20 (3H, t, *J* =6.9 Hz, CH_3), 1.61-1.70 (6H, m, CH_2), 3.40-3.46 (4H, m, CH_2) 3.50 (2H, q, *J* =6.9 Hz, CH_2), 4.56 (2H, s, CH_2, ^3J (^{77}Se-^{1}H) = 9.7 Hz), 6.95 (1H, s, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.1, 24.2, 25.1, 50.7, 64.5, 67.2, 128.6 [^1J (^{77}Se-^{13}C) = 93.5 Hz], 139.3, 175.5; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 545.6; Anal. Calcd for $C_{11}H_{18}N_2OSe$: C, 48.35; H, 6.64; N, 10.25. Found: C, 48.65; H, 6.79; N, 10.15.

5-(1-Ethoxyethyl)-2-piperidino-1,3-selenazole (3e) White solid. mp 54-56 ºC; IR (KBr): 2932, 1531 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.17 (3H, t, *J* =6.9 Hz, CH_3), 1.49 (3H, d, *J* =6.3 Hz, CH_3), 1.61-1.70 (6H, m, CH_2), 3.32-3.38 (1H, m, CH_2), 3.40-3.46 (4H, m, CH_2), 3.47-3.53 (1H, m, CH_2), 4.48 (1H, q, *J* =6.3 Hz, CH), 6.92 (1H, s, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.2, 24.1, 24.9, 25.1, 50.5,

63.1, 73.1, 136.0, 137.2, 174.3; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 522.1; Anal. Calcd for $C_{12}H_{20}N_2OSe$: C, 50.17; H, 7.02; N, 9.75. Found: C, 50.50; H, 7.14; N, 9.81.

5-(1-Ethoxypropyl)-2-piperidino-1,3-selenazole (3f) Orange solid. mp 37-38 ºC; IR (KBr): 2932, 1526 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* =6.9 Hz, CH_3), 1.17 (3H, t, *J* =6.3 Hz, CH_3), 1.59-1.70 (7H, m, CH_2), 1.87 (1H, sept, *J* = 6.9 Hz, CH), 3.30-3.36 (1H, m, CH_2), 3.40-3.46 (4H, m, CH_2) 3.51-3.57 (1H, m, CH_2), 4.14 (1H, t, *J* =6.3 Hz, CH), 6.92 (1H, s, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.3, 15.2, 24.2, 25.2, 31.8, 50.5, 63.3, 79.2, 134.7, 138.0, 174.6; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 522.5; Anal. Calcd for $C_{13}H_{22}N_2OSe$: C, 51.82; H, 7.36; N, 9.30. Found: C, 52.14; H, 7.46; N, 9.60.

5-(1-Ethoxy-1-methylethyl)-2-piperidino-1,3-selenazole (3g) Yellow liquid. IR (neat): 2934, 1528 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (3H, t, *J* =6.9 Hz, CH_3), 1.54 (6H, s, CH_3), 1.63-1.70 (6H, m, CH_2), 3.35 (2H, q, *J* =6.9 Hz, CH_2), 3.40-3.44 (4H, m, CH_2), 6.83 (1H, s, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.9, 24.2, 25.2, 28.8, 50.5, 58.1, 75.1, 136.4, 140.2, 174.6; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 539.1; Anal. Calcd for $C_{13}H_{22}N_2OSe$: C, 51.82; H, 7.36; N, 9.30. Found: C, 52.02; H, 7.74; N, 9.04.

5-Methoxymethyl-2-piperidino-1,3-selenazole (4a) Yellow liquid. IR (neat): 2933, 1526 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.63-1.70 (6H, m, CH_2), 3.32 (3H, s, CH_3), 3.42-3.48 (4H, m, CH_2), 4.50 (2H, s, CH_2, ^3J (^{77}Se-^{1}H) = 11.2 Hz), 6.97 (1H, s, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.1, 25.1, 50.6, 56.8, 69.0, 127.9, 139.6, 175.5; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 544.3; Anal. Calcd for $C_{10}H_{16}N_2OSe$: C, 46.34; H, 6.22; N, 10.81. Found: C, 46.20; H, 6.35; N, 10.91.

5-Isopropoxymethyl-2-piperidino-1,3-selenazole (4b) Yellow liquid. IR (neat): 2934, 1527 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.17 (6H, d, *J* = 6.3 Hz, CH_3), 1.63-1.69 (6H, m, CH_2), 3.40-3.43 (4H, m, CH_2), 3.71 (1H, sept, *J* = 6.3 Hz, CH), 4.56 (2H, s, CH_2, ^3J (^{77}Se-^{1}H) = 9.2 Hz), 6.94 (1H, s, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.0, 24.2, 25.1, 50.7, 64.6, 69.5, 129.4, 138.8, 175.4; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 546.9; Anal. Calcd for $C_{12}H_{20}N_2OSe$: C, 50.17; H, 7.02; N, 9.75. Found: C, 50.25; H, 7.28; N, 9.88.

5-*tert*-Butoxymethyl-2-piperidino-1,3-selenazole (4c) Orange solid. mp 47-49 ºC; IR (KBr): 2934, 1526 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (9H, s, CH_3), 1.62-1.67 (6H, m, CH_2), 3.38-3.43 (4H, m, CH_2), 4.49 (2H, s, CH_2), 6.93 (1H, s, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2, 25.1, 27.6, 50.6, 59.4, 73.6, 130.5, 137.7, 175.0; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 547.9; Anal. Calcd for $C_{13}H_{22}N_2OSe$: C, 51.82; H, 7.36; N, 9.30. Found: C, 51.96; H, 7.59; N, 9.18.

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