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PREPARATION OF 2-DIALKYLAMINO-1,3-SELENAZOLES BY REACTION OF *N,N*-UNSUBSTITUTED SELENOUREAS WITH α -DIKETONES

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

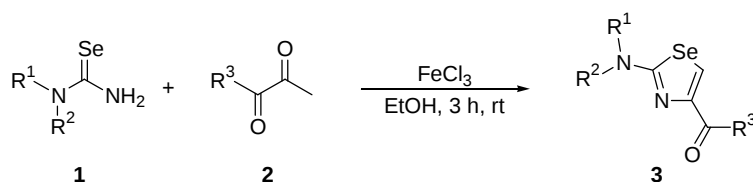
INTRODUCTION

Recently, syntheses of many types of 1,3-selenazoles are reported.¹ Some of them are studied as potential pharmaceutical and dye agents.² 2-Amino-1,3-selenazole derivatives induced the phosphorylation of extracellular receptor kinase. They also enhanced the phosphorylation of Akt, a signal transducing protein kinase for cell survival; and this phosphorylation was followed by suppression of cell death, thus suggesting that they had anti-apoptotic effects. They induced neurite outgrowth and facilitated the expression of neurofilament-M of PC12 cells, demonstrating that they induced neuronal differentiation of these cells. From the results of 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 types of 2-amino-1,3-selenazoles has been desired for the development of potential agents. For the synthesis of 2-amino-1,3-selenazoles, selenourea is one of the most useful starting material. For the synthesis of 2-amino-1,3-selenazole derivatives using selenoureas, several methods have been reported. For instance, reactions of selenourea with α -haloketones,⁴ chloroacetonitrile⁵ and α -haloacyl halides⁶ yielded the 2-amino-1,3-selenazoles. 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 or aldehydes in the

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

presence of ferric chloride without use of lachrymatory halo carbonyl compounds.⁷ In this studies, we describe the syntheses of 2-dialkylamino-1,3-selenazole derivatives by the reaction of *N,N*-unsubstituted selenoureas with α -carbonyl ketone derivatives.

RESULTS AND DISCUSSION



Scheme 1

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

Entry	Selenourea (1)	α -Diketone (2)	2-Amino-1,3-selenazole (3)	
			Compound	Yield (%) ^a
1	1a	2a	3a	90
2	1b	2a	3b	88
3	1c	2a	3c	80
4	1d	2a	3d	87
5	1d	2b	3e	80
6	1d	2c	3f	0
7	1d	2d	3g	70
			3h	77
8	1d	2e	3i	19

^a Isolated yield.

The most efficient conditions for the reaction of 1-selenocarbamoylpiperidine (**1d**) with 2,3-butanedione (**2d**) were investigated. 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-selenazoles in high yields.^{7a} In the present reaction, room temperature was the best conditions. The reactions of **1d** with **2a** in the presence of ferric chloride at room temperature gave ethyl 2-piperidino-1,3-selenazole-4-carboxylate (**3d**) in 87% yield (Scheme 1). The structure of **3d** was elucidated by studies of IR, ¹H-, ¹³C-, ⁷⁷Se-NMR and elemental analysis. Reactions of *N,N*-unsubstituted selenoureas (**1a-1d**) with **2a** gave the corresponding 2-amino-1,3-selenazole-4-carboxylates (**3a-3d**) in 80-90% yields (Table 1, Entries 1-4). Using the optimal reaction conditions, several 2-amino-1,3-selenazole derivatives (**3a-3i**) were prepared from the reactions of corresponding *N,N*-unsubstituted selenoureas (**1a-1d**) with several α -diketone derivatives (**2a-2e**) in the presence of ferric chloride at room temperature (Table 1). The structures of products (**3a-3i**) were determined by comparing the spectral data with those of **3d**. Reaction with pyruvic acid (**2c**) did not proceed (Table 1, Entry 6). Reaction with 2,3-pentadione (**2e**) gave two compounds, 4-acetyl-5-methyl-2-piperidino-1,3-selenazole (**3h**) was predominant (Table 1, Entry 8).

In the present study, we confirmed that the reactions of *N,N*-unsubstituted selenoureas (**1**) with α -diketone derivatives (**2**) in alcohol in the presence of ferric chloride at room temperature give several type of 2-dialkylamino-1,3-selenazole derivatives (**3**) for the first time.

EXPERIMENTAL

General

Selenoureas were synthesized according to previously described procedures.⁸ The ⁷⁷Se chemical shifts are expressed in ppm deshielded with respect to Me₂Se in CDCl₃. ²J (⁷⁷Se-¹H), ³J (⁷⁷Se-¹H) values and ¹J (⁷⁷Se-¹³C) values are the ⁷⁷Se satellites of the ¹H NMR spectra and proton-decoupled ¹³C NMR spectra, respectively.

General procedure for synthesis of ethyl 2-dimethylamino-1,3-selenazole-4-carboxylate (3a). Ethyl pyruvate (**2a**) (0.28 ml, 2.5 mmol) was added to stirred solution of *N,N*-dimethylselenourea (**1a**) (75 mg, 0.5 mmol) in dry ethanol (5 mL) under an argon atmosphere. Ferric chloride (0.47 g, 3.0 mmol) was added into the reaction mixture. The reaction mixture was stirred for 3 h under room temperature. The mixture was diluted with ethyl acetate and saturated Na₂CO₃ 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** (222.4 mg, 90%) as yellow solid. Mp 37–39 °C. IR (KBr): 2905, 1718, 1569 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.36 (3H, t, *J* = 7.2 Hz, CH₃), 3.13 (6H, s,

CH₃), 4.33 (2H, q, $J = 7.2$ Hz, CH₂), 8.02 (1H, s, CH) [$^2J(^{77}\text{Se}-^1\text{H}) = 49.3$ Hz]; ^{13}C NMR (125 MHz, CDCl₃): δ 14.1, 41.0, 60.7, 120.9 [$^1J(^{77}\text{Se}-^{13}\text{C}) = 105.6$ Hz], 145.4, 161.8, 172.2; ^{77}Se (95 MHz, CDCl₃): δ 589.5; Anal. Calcd for C₈H₁₂N₂O₂Se: C, 38.88; H, 4.89; N, 11.33. Found; C, 39.10; H, 5.13; N, 10.98.

Ethyl 2-diethylamino-1,3-selenazole-4-carboxylate (3b) Yellow liquid. IR (neat): 2975, 1726, 1553 cm⁻¹; ^1H NMR (500 MHz, CDCl₃): δ 1.24 (6H, t, $J = 6.9$ Hz, CH₃), 1.36 (3H, t, $J = 6.9$ Hz, CH₃), 3.51 (4H, q, $J = 6.9$ Hz, CH₂), 4.33 (2H, q, $J = 6.9$ Hz, CH₂), 7.98 (1H, s, CH) [$^2J(^{77}\text{Se}-^1\text{H}) = 49.3$ Hz]; ^{13}C NMR (125 MHz, CDCl₃): δ 12.3, 14.1, 46.1, 60.6, 119.9 [$^1J(^{77}\text{Se}-^{13}\text{C}) = 105.6$ Hz], 145.3, 161.8, 170.7; ^{77}Se (95 MHz, CDCl₃): δ 588.0; Anal. Calcd for C₁₀H₁₆N₂O₂Se: C, 43.64; H, 5.86; N, 10.18. Found; C, 43.77; H, 6.04; N, 9.96.

Ethyl 2-morpholino-1,3-selenazole-4-carboxylate (3c) Orange solid. Mp 81-83 °C. IR (KBr): 2931, 1702, 1550 cm⁻¹; ^1H NMR (500 MHz, CDCl₃): δ 1.36 (3H, t, $J = 7.2$ Hz, CH₃), 3.51 (4H, t, $J = 5.2$ Hz, CH₂), 3.80 (4H, t, $J = 5.2$ Hz, CH₂), 4.33 (2H, q, $J = 7.2$ Hz, CH₂), 8.12 (1H, s, CH) [$^2J(^{77}\text{Se}-^1\text{H}) = 49.3$ Hz]; ^{13}C NMR (125 MHz, CDCl₃): δ 14.1, 49.5, 60.9, 65.9, 121.8 [$^1J(^{77}\text{Se}-^{13}\text{C}) = 105.6$ Hz], 145.2, 161.6, 173.1 [$^1J(^{77}\text{Se}-^{13}\text{C}) = 123.6$ Hz]; ^{77}Se (95 MHz, CDCl₃): δ 599.3; Anal. Calcd for C₁₀H₁₄N₂O₃Se: C, 41.53; H, 4.88; N, 9.69. Found; C, 41.89; H, 5.15; N, 9.29.

Ethyl 2-piperidino-1,3-selenazole-4-carboxylate (3d) Yellow solid. Mp 52-54 °C. IR (KBr): 2931, 1712, 1548 cm⁻¹; ^1H NMR (500 MHz, CDCl₃): δ 1.36 (3H, t, $J = 7.2$ Hz, CH₃), 1.62-1.70 (6H, m, CH₂), 3.44-3.51 (4H, m, CH₂), 4.32 (2H, q, $J = 7.2$ Hz, CH₂), 8.04 (1H, s, CH) [$^2J(^{77}\text{Se}-^1\text{H}) = 49.8$ Hz]; ^{13}C NMR (125 MHz, CDCl₃): δ 14.2, 23.9, 25.1, 50.7, 60.8, 120.8 [$^1J(^{77}\text{Se}-^{13}\text{C}) = 105.7$ Hz], 145.2, 161.8, 172.9 [$^1J(^{77}\text{Se}-^{13}\text{C}) = 122.4$ Hz]; ^{77}Se (95 MHz, CDCl₃): δ 592.8; Anal. Calcd for C₁₁H₁₆N₂O₂Se: C, 46.00; H, 5.61; N, 9.75. Found; C, 46.27; H, 5.89; N, 9.68.

Methyl 2-piperidino-1,3-selenazole-4-carboxylate (3e) Pale yellow solid. Mp 55-57 °C. IR (KBr): 2934, 1712, 1523 cm⁻¹; ^1H NMR (500 MHz, CDCl₃): δ 1.62-1.71 (6H, m, CH₂), 3.46-3.51 (4H, m, CH₂), 3.86 (3H, s, CH₃), 8.07 (1H, s, CH) [$^2J(^{77}\text{Se}-^1\text{H}) = 49.3$ Hz]; ^{13}C NMR (125 MHz, CDCl₃): δ 24.0, 25.1, 50.8, 52.1, 121.2 [$^1J(^{77}\text{Se}-^{13}\text{C}) = 106.8$ Hz], 144.9, 162.5, 177.3.1; ^{77}Se (95 MHz, CDCl₃): δ 593.8; Anal. Calcd for C₁₀H₁₄N₂O₂Se: C, 43.96; H, 5.17; N, 10.25. Found; C, 44.11; H, 5.40; N, 9.91.

4-Acetyl-2-piperidino-1,3-selenazole (3g) Orange crystals. Mp 57-58 °C. IR (KBr): 2937, 1679, 1558 cm⁻¹; ^1H NMR (500 MHz, CDCl₃): δ 1.64-1.72 (6H, m, CH₂), 2.53 (3H, s, CH₃), 3.45-3.51 (4H, m, CH₂), 8.03 (1H, s, CH) [$^2J(^{77}\text{Se}-^1\text{H}) = 49.2$ Hz]; ^{13}C NMR (125 MHz, CDCl₃): δ 24.1, 25.1, 27.7, 50.8, 119.9 [$^1J(^{77}\text{Se}-^{13}\text{C}) = 108.0$ Hz], 153.5, 172.6 [$^1J(^{77}\text{Se}-^{13}\text{C}) = 124.8$ Hz], 193.2; ^{77}Se NMR (95 MHz, CDCl₃): δ 600.3; Anal. Calcd for C₁₀H₁₄N₂OSe: C, 46.70; H, 5.49; N, 10.89. Found; C, 46.64; H, 5.71; N, 10.524.

4-Acetyl-5-methyl-2-piperidino-1,3-selenazole (3h) Yellow solid. Mp 43-45 °C. IR (KBr): 2935, 1672, 1546 cm⁻¹; ^1H NMR (500 MHz, CDCl₃): δ 1.62-1.69 (6H, m, CH₂), 2.53 (3H, s, CH₃), 2.70 (3H, s, CH₃)

$[^3J(^{77}\text{Se}-^1\text{H}) = 11.5 \text{ Hz}]$, 3.36-3.41 (4H, m, CH_2); ^{13}C NMR (125 MHz, CDCl_3): δ 15.0 [$^2J(^{77}\text{Se}-^{13}\text{C}) = 19.2 \text{ Hz}$], 24.2, 25.1, 30.0, 50.5, 139.8, 146.5, 167.6, 196.2; ^{77}Se NMR (95 MHz, CDCl_3): δ 648.8; Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{OSe}$: C, 48.71; H, 5.95; N, 10.33. Found; C, 48.69; H, 6.17; N, 10.12.

2-Piperidino-4-propionyl-1,3-selenazole (3i) Orange solid. Mp 52-54 °C. IR (KBr): 2930, 1679, 1546 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 1.16 (3H, t, $J = 7.2 \text{ Hz}$, CH_3) 1.64-1.72 (6H, m, CH_2), 2.96 (2H, q, $J = 7.2 \text{ Hz}$, CH_2), 3.46-3.50 (4H, m, CH_2), 8.02 (1H, s, CH) [$^2J(^{77}\text{Se}-^1\text{H}) = 49.8 \text{ Hz}$]; ^{13}C NMR (125 MHz, CDCl_3): δ 8.23, 24.2, 25.2, 33.5, 50.9, 119.2, 153.2, 172.8, 196.5; ^{77}Se NMR (95 MHz, CDCl_3): δ 595.3. Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{OSe}$: C, 48.71; H, 5.95; N, 10.33. Found; C, 48.68; H, 6.01; N, 10.13.

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