HETEROCYCLES, Vol. 74, 2007, pp.1009 - 1014. © The Japan Institute of Heterocyclic Chemistry
Received, 12th September, 2007, Accepted, 12th October, 2007, Published online, 16th October, 2007. COM-07-S(W)71

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

Koichi Kanoh,[a] Hideharu Ishihara,[a] and Mamoru Koketsu[b,*]

[a]Department of Chemistry, Faculty of Engineering, Gifu University, Gifu 501-1193, Japan
[b]Division of Instrumental Analysis, Life Science Research Center, Gifu University, Gifu 501-1193, Japan
koketsu@gifu-u.ac.jp

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.

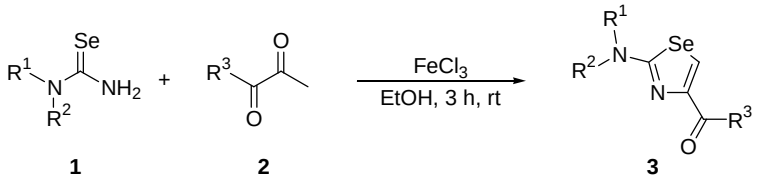
INTRODUCTION

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] chloroacetonitrile[5] and α-haloacyl halides[6] 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.

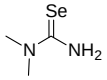
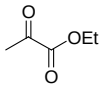
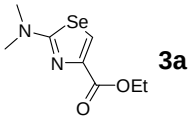
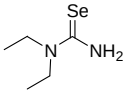
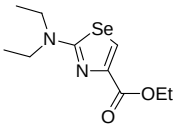
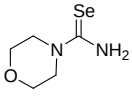
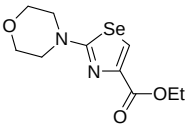
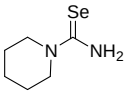
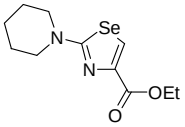
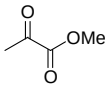
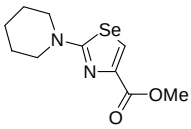
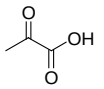
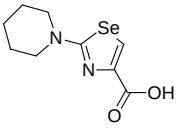
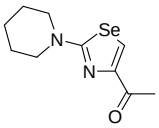
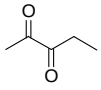
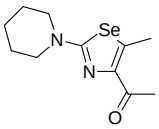
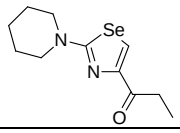
RESULTS AND DISCUSSION



1 **2** **3**

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
8	**1d**	 **2e**	 **3h**	77
			 **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-selnazoles 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, ^{1}H-, ^{13}C-, ^{77}Se-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 ^{77}Se chemical shifts are expressed in ppm deshielded with respect to Me_2Se in $CDCl_3$. ^{2}J (^{77}Se-^{1}H), ^{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 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 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** (222.4 mg, 90%) as yellow solid. Mp 37–39 °C. IR (KBr): 2905, 1718, 1569 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (3H, t, J = 7.2 Hz, CH_3), 3.13 (6H, s,

CH_3), 4.33 (2H, q, J = 7.2 Hz, CH_2), 8.02 (1H, s, CH) [^2J (^{77}Se-^{1}H) = 49.3 Hz]; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 41.0, 60.7, 120.9 [^1J (^{77}Se-^{13}C) = 105.6 Hz], 145.4, 161.8, 172.2; ^{77}Se (95 MHz, $CDCl_3$): δ 589.5; Anal. Calcd for $C_8H_{12}N_2O_2Se$: 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}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (6H, t, J = 6.9 Hz, CH_3), 1.36 (3H, t, J = 6.9 Hz, CH_3), 3.51 (4H, q, J = 6.9 Hz, CH_2), 4.33 (2H, q, J = 6.9 Hz, CH_2), 7.98 (1H, s, CH) [^2J (^{77}Se-^{1}H) = 49.3 Hz]; ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.3 14.1, 46.1, 60.6, 119.9 [^1J (^{77}Se-^{13}C) = 105.6 Hz], 145.3, 161.8, 170.7; ^{77}Se (95 MHz, $CDCl_3$): δ 588.0; Anal. Calcd for $C_{10}H_{16}N_2O_2Se$: 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}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (3H, t, J = 7.2 Hz, CH_3), 3.51 (4H, t, J = 5.2 Hz, CH_2), 3.80 (4H, t, J = 5.2 Hz, CH_2), 4.33 (2H, q, J = 7.2 Hz, CH_2), 8.12 (1H, s, CH) [^2J (^{77}Se-^{1}H) = 49.3 Hz]; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 49.5, 60.9, 65.9, 121.8 [^1J (^{77}Se-^{13}C) = 105.6 Hz], 145.2, 161.6, 173.1 [^1J (^{77}Se-^{13}C) = 123.6 Hz]; ^{77}Se (95 MHz, $CDCl_3$): δ 599.3; Anal. Calcd for $C_{10}H_{14}N_2O_3Se$: 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}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (3H, t, J = 7.2 Hz, CH_3), 1.62-1.70 (6H, m, CH_2), 3.44-3.51 (4H, m, CH_2), 4.32 (2H, q, J = 7.2 Hz, CH_2), 8.04 (1H, s, CH) [^2J (^{77}Se-^{1}H) = 49.8 Hz]; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 23.9, 25.1, 50.7, 60.8, 120.8 [^1J (^{77}Se-^{13}C) = 105.7 Hz], 145.2, 161.8, 172.9 [^1J (^{77}Se-^{13}C) = 122.4 Hz]; ^{77}Se (95 MHz, $CDCl_3$): δ 592.8; Anal. Calcd for $C_{11}H_{16}N_2O_2Se$: 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}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.62-1.71 (6H, m, CH_2), 3.46-3.51 (4H, m, CH_2), 3.86 (3H, s, CH_3), 8.07 (1H, s, CH) [^2J (^{77}Se-^{1}H) = 49.3 Hz]; ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.0, 25.1, 50.8, 52.1, 121.2 [^1J (^{77}Se-^{13}C) = 106.8 Hz], 144.9, 162.5, 177.3.1; ^{77}Se (95 MHz, $CDCl_3$): δ 593.8; Anal. Calcd for $C_{10}H_{14}N_2O_2Se$: 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}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.64-1.72 (6H, m, CH_2), 2.53 (3H, s, CH_3), 3.45-3.51 (4H, m, CH_2), 8.03 (1H, s, CH) [^2J (^{77}Se-^{1}H) = 49.2 Hz]; ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.1, 25.1, 27.7, 50.8, 119.9 [^1J (^{77}Se-^{13}C) = 108.0 Hz], 153.5, 172.6 [^1J (^{77}Se-^{13}C) = 124.8 Hz], 193.2; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 600.3; Anal. Calcd for $C_{10}H_{14}N_2OSe$: 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}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.62-1.69 (6H, m, CH_2), 2.53 (3H, s, CH_3), 2.70 (3H, s, CH_3)

[^3J (^{77}Se-^{1}H) = 11.5 Hz], 3.36-3.41 (4H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.0 [^2J (^{77}Se-^{13}C) = 19.2 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 $C_{11}H_{16}N_2OSe$: 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}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (3H, t, J = 7.2 Hz, CH_3) 1.64-1.72 (6H, m, CH_2), 2.96 (2H, q, J = 7.2 Hz, CH_2), 3.46-3.50 (4H, m, CH_2), 8.02 (1H, s, CH) [^2J (^{77}Se-^{1}H) = 49.8 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 $C_{11}H_{16}N_2OSe$: C, 48.71; H, 5.95; N, 10.33. Found; C, 48.68; H, 6.01; N, 10.13.

ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Science Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 17550099) to which we are grateful.

REFERENCES

1. (a) A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Comprehensive Heterocyclic Chemistry II, Vols. 1-11; Pergamon Press, Inc., New York, 1996. (b) T. G. Back, Organoselenium Chemistry: A Practical Approach, Oxford University Press, 1999. (c) K. Geisler, W.-D. Pfeiffer, A. Künzler, H. Below, E. Bulka, and P. Langer, *Synthesis*, 2004, 875. (d) M. Narender, M. S. Reddy, V. P. Kumar, V. V. P. Reddy, Y. V. D. Nageswar, and K. R. Rao, *J. Org. Chem.*, 2007, **72**, 1849.
2. (a) D. Keil and H. Hartmann. *Dyes and Pigm.*, 2000, **44**, 149. (b) D. Keil, H. Hartmann, I. Zug, and A. Schroder, *J. Prakt. Chem.*, 2000, **42**, 169. (c) M. Koketsu, S. Y. Choi, H. Ishihara, B. O. Lim, H. Kim, and S. Y. Kim, *Chem. Pharm. Bull.*, 2002, **50**, 1594.
3. A. Nishina, A. Sekiguchi, R. Fukumoto, M. Koketsu, and S. Furukawa, *Biochem. Biophys. Res. Commun.*, 2007, **352**, 360.
4. (a) W. D. Pfeiffer and E. Bulka, *Chemiker-Zeitung*, 1991, **115**, 361. (b) A. Shafiee and M. Rezayazdi, *J. Heterocycl. Chem.*, 1995, **32**, 177. (c) A. M. Farag, K. M. Dawood, Z. E. Kandeel, and M. S. Algharib, *J. Chem. Res. (S)*, 1996, 530. (d) A. Shafiee, M. A. Ebrahimzadeh, and A. Maleki, *J. Heterocycl. Chem.*, 1999, **36**, 901. (e) D. Keil and H. Hartmann, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1999, **152**, 169.
5. M. Koketsu, H. Tanaka, and H. Ishihara, *Chem. Lett.*, 2005, **34**, 1260.
6. M. Koketsu, F. Nada, and H. Ishihara, *Synthesis*, 2002, 195.
7. (a) M. Koketsu, K. Kanoh, H. Ando, and H. Ishihara, *Heteroatom Chem.*, 2006, **17**, 88. (b) M.

Koketsu, K. Kanoh, and H. Ishihara, *Heterocycles*, 2006, **68**, 2145. (c) M. Koketsu, K. Kanoh, and H. Ishihara, *Heterocycles*, 2006, **68**, 2647.

8. (a) M. Koketsu, Y. Fukuta, and H. Ishihara, *Tetrahedron Lett.*, 2001, **42**, 6333. (b) M. Koketsu, N. Takakura, and H. Ishihara, *Synth. Commun.*, 2002, **32**, 3075.