Synthesis of 1,3-Selenazines and 1,3-Selenazolidines via Intramolecular Addition of *N*-Allylselenoureas

Mamoru Koketsu,*[1] Takashi Kiyokuni,[2] Tsutomu Sakai,[2] Hiromune Ando,[1] and Hideharu Ishihara*[2]
[1]*Division of Instrumental Analysis, Life Science Research Center, Gifu University, Gifu 501-1193*
[2]*Department of Chemistry, Faculty of Engineering, Gifu University, Gifu 501-1193*

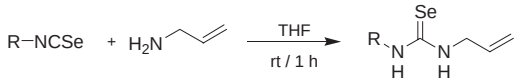
(Received March 16, 2006; CL-060322; E-mail: koketsu@cc.gifu-.ac.jp)

The regiochemistry of intramolecular addition of *N*-allylselenoureas leading to 2-imino-5-methyl-1,3-selenazolidines or 2-amino-5-iodo-4*H*-5,6-dihydro-1,3-selenazines depends on the treatment of hydrogen chloride or iodine: treatment of hydrogen chloride with *N*-allylselenoureas affords preferentially 2-imino-5-methyl-1,3-selenazolidines through 5-*endo* closure, whereas treatment of iodine affords preferentially 2-amino-5-iodo-4*H*-5,6-dihydro-1,3-selenazines through 6-*exo* closure.

Selenium–nitrogen heterocycles such as 1,3-selenazines and 1,3-selenazoles have enthusiastically been studied in the fields of chemistry[1] and pharmaceutical science, because they biologically act as antioxidants and can inhibit human fibro sarcoma DNA fragmentation, eukaryotic elongation factor-2 kinase and inducible nitric oxide production.[2] Several reactions using *N*-allylthioureas, *N*-homoallyl-thioamides and -thioureas have been reported. For example, *N*-allylthioureas by enzymic treatment[3] or active manganese dioxide[4] converted to the corresponding ureas. By an iodocyclization of *N*-allylthioureas, 4,5-dihydro-1,3-thiazoles were obtained.[5] The 6-iodomethyl-5,6-dihydro-4*H*-1,3-thiazines were prepared by iodocyclization of *N*-homoallylthioamides.[6] 2-Amino- or 2-imino-1,3-thiazole derivatives were obtained by cyclization of *N*-allylthioureas with hydrogen chloride.[7] In contrast, there are few reports on the synthesis of selenium–nitrogen heterocycles using *N*-allylselenoureas[8] by iodocyclization and cyclization with hydrogen chloride. Herein, preparation of 1,3-selenazine and 1,3-selenazole derivatives from *N*-allylselenoureas has been described.

Five kinds of *N*-allylselenoureas **1** were prepared by reactions of isoselenocyanates with allylamine (Scheme 1).[9]

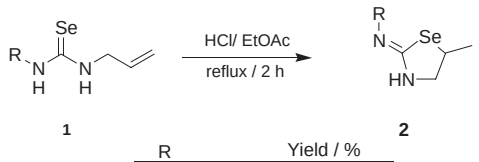
Next, we investigated synthesis of selenium–nitrogen heterocycles via intramolecular addition using obtained *N*-allylselenoureas **1**. Reaction of *N*-allyl-*N*′-*p*-tolylselenourea (**1b**) with dry hydrogen chloride under reflux conditions (bath temp: 80 °C) gave 5-methyl-2-*p*-tolylimino-1,3-selenazolidine (**2b**) in quantitative yield (Scheme 2). Under the optimal reaction conditions, five kinds of five-membered ring 2-imino-5-methyl-1,3-selenazolidines **2a**–**2e**[10] were prepared by reactions using *N*-allylselenoureas **1** with hydrogen chloride in high yields



R	Yield (%)
C_6H_5	95 (**1a**)
4-$CH_3C_6H_4$	89 (**1b**)
4-ClC_6H_4	98 (**1c**)
2-Naphtyl	95 (**1d**)
cyclo-C_6H_{11}	97 (**1e**)

1

Scheme 1.



1 **2**

R	Yield / %
C_6H_5	81 (**2a**)
4-$CH_3C_6H_4$	Quant. (**2b**)
4-ClC_6H_4	95 (**2c**)
2-Naphthyl	92 (**2d**)
cyclo-C_6H_{11}	Quant. (**2e**)

Scheme 2.

(Scheme 2). The driving force, in this case, is the formation of the more stable carbonium ion. This behavior is in agreement with the cyclization of imidates, amides, and carbonates, which afford five-membered heterocyclic rings exclusively.[11]

Crystal structure of the 2-(2-naphthyl)imino-5-methyl-1,3-selenazolidine (**2d**) was determined by X-ray diffraction analysis (Figure 1).[12] Though the isomeric 2-amino-5-methyl-4,5-dihydro-1,3-selenazole is a possible product, the structure of **2** was confirmed to be 2-imino-5-methyl-1,3-selenazolidine by crystal analysis of **2d**.

Furthermore, we studied iodocyclization of *N*-allylselenoureas **1**. Reaction of *N*-allyl-*N*′-phenylselenourea (**1a**) with iodine afforded 5-iodo-2-phenylamino-4*H*-5,6-dihydro-1,3-selenazine (**3a**) in 90% yield at room temperature (Scheme 3).[13] The structure of **3a** was elucidated by studies of IR, ^{1}H, ^{13}C, ^{77}Se NMR, COSY, HMQC, and HMBC data, MS, and HRMS. Under the same reaction conditions, four kinds of *N*-allylselenoureas **1** were treated with iodine to give the corresponding 2-amino-5-iodo-1,3-selenazine **3** in moderate to high yields (Scheme 3). Reaction at −40 °C also resulted in the formation of only six-membered ring compound **3** while formation of five-membered ring compound has not been observed. Previously, reactions of intramolecular iodocyclization of allylureas and allylthioureas gave the corresponding five-membered ring 4,5-dihydro-1,3-oxazoles and 4,5-dihydro-1,3-thiazoles, respectively.[5,14] Reactions with *N*-homoallyl-thioamides and -thioamides afforded six-mem-

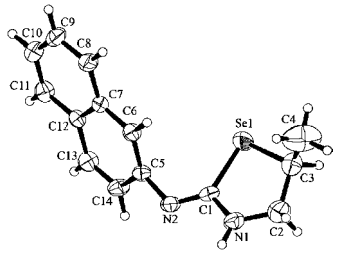
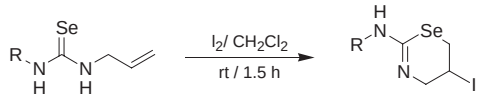


Figure 1. ORTEP diagram (50% thermal ellipsoids) of 2-(2-naphthyl)imino-5-methyl-1,3-selenazolidine (**2d**).



1 3

R	Yield / %
C_6H_5	90 (**3a**)
4-$CH_3C_6H_4$	76 (**3b**)
4-ClC_6H_4	53 (**3c**)
cyclo-C_6H_{11}	96 (**3d**)

Scheme 3.

bered ring 6-iodomethyl-4*H*-5,6-dihydro-1,3-thiazines.[5,6] The present reactions with *N*-allylselenoureas **1** gave six-membered ring 5-iodo-4*H*-5,6-dihydro-1,3-selenazines **3** by iodocyclization.

In this letter, we confirmed intramolecular addition of *N*-allylselenoureas afforded five-membered ring 1,3-selenazolidines through 5-*endo* closure or six-membered ring 1,3-selenazines through 6-*exo* closure by treatment of hydrogen chloride or iodine, respectively.

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9 Typical spectral data for **1**. *N*-Allyl-*N*′-(2-naphthyl)selenourea (**1d**): IR (KBr): 1634, 1536 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.37 (2H, s), 5.13–5.18 (2H, m), 5.82–5.91 (1H, m), 6.45 (1H, br), 7.33–7.91 (7H, m), 9.19 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$): δ 50.2, 117.2, 123.1, 123.3, 126.5, 126.9, 127.5, 127.6, 130.2, 131.8, 132.6, 132.8, 133.4, 178.6; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 211.6; MS (FAB): m/z 291 [$M^+ + 1$]; Anal. Calcd for $C_{14}H_{14}N_2Se$: C, 58.14; H, 4.88; N, 9.69%. Found: C, 58.52; H, 5.13; N, 9.58%.

10 Synthesis procedure and spectral data of selected compounds. 2-*p*-Tolylimino-5-methyl-1,3-selenazolidine (**2b**): 1 M Hydrogen chloride in diethyl ether solution (0.52 mL, 0.52 mmol) was added to an ethyl acetate solution (5 mL) of *N*-allyl-*N*′-*p*-tolylselenourea (**1b**) (25.4 mL, 0.10 mmol). The reaction mixture was stirred for 2 h in an oil bath kept at 80 °C. The mixture was extracted with dichloromethane, washed with aqueous saturated sodium carbonate. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with dichloromethane/methanol (30/1) as the eluent to give **2b** (25.2 mg, quantitative yield). IR (KBr): 1600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.54 (3H, d, $J = 6.9$ Hz), 2.30 (3H, s), 3.32 (1H, dd, $J = 6.6$, 10.9 Hz), 3.72 (1H, dd, $J = 5.7$, 10.9 Hz), 3.91–3.98 (1H, m), 6.75 (1H, brs), 6.91 (2H, d, $J = 8.6$ Hz), 7.08 (2H, d, $J = 8.6$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 20.9, 39.1, 55.9, 121.2, 129.5, 132.8, 147.9, 161.0; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 411.5; MS (FAB): m/z 255 [$M^+ + 1$]; Anal. Calcd for $C_{11}H_{14}N_2Se$: C, 52.18; H, 5.57; N, 11.06%. Found: C, 52.03; H, 5.62; N, 10.79%.

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12 For **2d**. CCDC 601464 contains the supplementary crystallographic data for this letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

13 Synthesis procedure and spectral data of selected compounds. 5-Iodo-2-*p*-tolylamino-4*H*-5,6-dihydro-1,3-selenazine (**3b**): Iodine (76.3 mg, 0.30 mmol) was added to a dichloromethane solution (13.0 mL) of *N*-allyl-*N*′-*p*-tolylselenourea (**1b**) (76.0 mg, 0.30 mmol). The reaction mixture was stirred at room temperature for 1.5 h. The mixture was extracted with dichloromethane, washed with aqueous saturated sodium carbonate. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with dichloromethane/ether (25/1) as the eluent to give **3b** (86.6 mg, 76%). IR (KBr): 1626 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.31 (3H, s), 3.53 (1H, dd, $J = 4.0$, 9.7 Hz), 3.60 (1H, m), 3.77 (1H, dd, $J = 5.7$, 12.0 Hz), 3.85 (1H, dd, $J = 2.9$, 12.0 Hz), 4.11–4.17 (1H, m), 6.93 (2H, d, $J = 8.6$ Hz), 7.09 (2H, d, $J = 8.6$ Hz), 7.35 (1H, brs); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.3, 20.9, 44.5, 54.4, 121.2, 129.8, 133.9, 145.8, 159.7; MS (EI): m/z 380 [M^+]; HRMS: m/z 379.9289, calcd for $C_{11}H_{13}IN_2Se$, found 379.9301.

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