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SYNTHESIS OF 2-AMINO-4,5-DIHYDRO-1,3-SELENAZOL-4-ONES BY REACTION OF *N,N*-DISUBSTITUTED SELENOUREAS WITH ACETYLENEDICARBOXYLATE

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Abstract – Reaction of *N,N*-disubstituted selenoureas with dimethyl acetylenedicarboxylate afforded 2-amino-5-methoxycarbonylmethylene-4,5-dihydro-1,3-selenazol-4-ones in high yields. The crystal structure of 5-methoxycarbonylmethylene-2-piperidino-4,5-dihydro-1,3-selenazol-4-one was confirmed by X-Ray diffraction. Reaction of the *N,N*-disubstituted selenoureas with acetylenedicarboxylic acid gave 2-amino-5-carboxymethylene-4,5-dihydro-1,3-selenazol-4-ones in high yields.

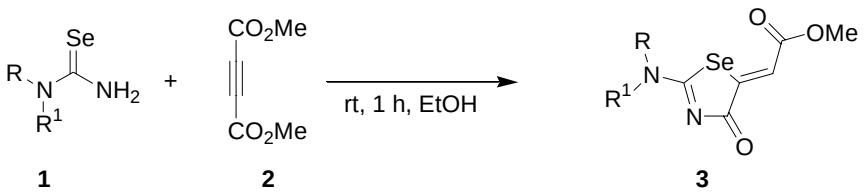
INTRODUCTION

Many syntheses of selenium-containing heterocyclic compounds have been reported.[1] Recently, the synthesis of selenium-containing heterocycles has been extensively studied using the carbon-selenium double bond as 2π dienophile intermediates for [4+2] cycloadditions. For example, the reaction of selenoazadiene with dimethyl acetylenedicarboxylate (DMAD) affords a 4*H*-selenazine, six-membered ring compound, that converts to a 4*H*-selenopyran by cycloreversion and recycloaddition with excess DMAD.[2] Furthermore, six-membered, 2-iminoperhydro-1,3-selenazin-4-ones were synthesized by the reaction of *N,N'*-disubstituted selenoureas with acryloyl chloride.[3] On the other hand, five-membered ring 4,5-dihydro-1,3-selenazol-4-ones**,** are obtained by a cycloaddition and intramolecular substitution between selenoazadiene and DMAD.[4] Recently, we reported synthesis of 2-aryl-5-methoxycarbonylmethylene-4,5-dihydro-1,3-selenazol-4-ones by reactions of primary selenoamides with DMAD and synthesis of 2-aryl-4-ethoxy-5-carboxymethylene-4,5-dihydro-

1,3-selenazol-4-ols by reactions of the primary selenoamides with acetylenedicarboxylic acid in ethanol solvent.[5] Thus, utility of the compounds bearing carbon-selenium double bond as 2π dienophiles such as selenoamides, selenoureas and selenazadienes could supply prospects for a variety of selenium-containing heterocycles.[6] We reported a new route to 2-amino-1,3-selenazoles by reactions of *N*,*N*-unsubstituted selenoureas with ketones and α,β-unsaturated ketones in the presence of ferric chloride without use of lachrymatory halo carbonyl compounds.[7] And also 5-acyl-2-amino-1,3-selenazoles have obtained by reaction of selenazadienes with α-haloketones.[8] Among the 2-amino-1,3-selenazoles, 2-piperidino-1,3-selenazole, 4-phenyl-2-piperidino-1,3-selenazole and bis[2-dimethylamino-5-(1,3-selenazolyl)] ketone exhibited the strong superoxide anion-scavenging activity among the 2-amino-1,3-selenazoles. These compounds acted *in vitro* as effective O_2^- scavengers.[9] Therefore, the preparation of many kinds of 2-amino-1,3-selenazoles has been desired for the development of potential agents. Herein, we describe the syntheses of 2-amino-5-carbonylmethylene-4,5-dihydro-1,3-selenazol-4-ones using *N*,*N*-disubstituted selenoureas.

RESULTS AND DISCUSSION

N,*N*-Disubstituted selenoureas (**1a**-**1d**) were prepared by previous reported method.[10] We first examined the reaction in alcoholic solvent. During the course of the screening of a variety of reaction conditions such as reaction temperature, reaction time and solvents, we found ethanol was found to be superior in terms of yield, reaction time and easy isolation of products compared with other solvents. DMAD (**2**) was added to a solution of piperidinocarboselenoamide (**1c**) in ethanol and the mixture was stirred at room temperature for 1 hour. 5-Methoxycarbonylmethylene-2-piperidino-4,5-dihydro-1,3-selenazol-4-one (**3c**)[11] was obtained in 88% yield. Three other 2-amino-5-methoxycarbonylmethylene-4,5-dihydro-1,3-selenazol-4-ones (**3**) were prepared by reactions of *N*,*N*-disubstituted selenoureas (**1**) with DMAD (**2**) in high yields (84-90%, Scheme 1).



1 **2** **3**

R	R^1	Yield (%)
CH_3	CH_3	84 (**3a**)
C_2H_5	C_2H_5	88 (**3b**)
—$(CH_2)_5$—		88 (**3c**)
—$(CH_2)_2O(CH_2)_2$—		90 (**3d**)

Scheme 1

The structure of 5-methoxycarbonylmethylene-2-piperidino-4,5-dihydro-1,3-selenazol-4-one (**3c**) was elucidated by studies of IR, ^{1}H-, ^{13}C-, ^{77}Se-NMR and elemental analysis.[12] In order to confirm the crystal structure of **3c**, we carried out the X-ray analysis of this compound. An ORTEP drawing, depicted in Figure 1, shows the molecular structure of the **3c**.[13] The bond angle the selenium atom C6-Se1-C4 was 83.6(1)°, consistent with the previous reported value.[14] It was confirmed that double bond of **3c** is *Z* configuration.

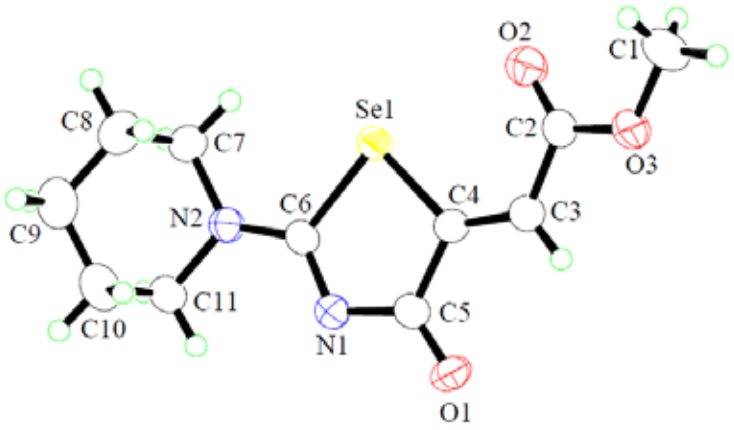
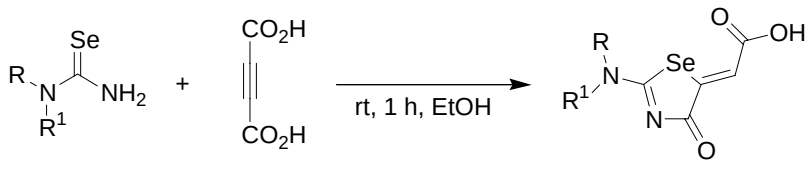


Figure 1. Crystal structure of 5-methoxycarbonylmethylene-2-piperidino-4,5-dihydro-1,3-selenazol-4-one (3c)

Next, reactions of **1** with acetylenedicarboxylic acid (**4**) were studied. The reaction afforded 2-amino-5-carboxymethylene-4,5-dihydro-1,3-selenazol-4-ones (**5**) in high yields (95-99%, Scheme 2). In the case of reactions using primary selenoamides,[5] ethoxy group at C4 position was introduced by the nucleophilic addition of oxygen of ethanol solvent, whilst this reaction gave more stable resonance structure, 2-amino-5-carboxymethylene-4,5-dihydro-1,3-selenazol-4-ones (**5**), instead of 2-aryl-4-ethoxy-5-carboxymethylene-4,5-dihydro-1,3-selenazol-4-ols bearing ethoxy group at C4 position. It seems to be contribution of electron lone pair of nitrogen at 2-amino group for the stability compared with reactions using primary selenoamides.[5]

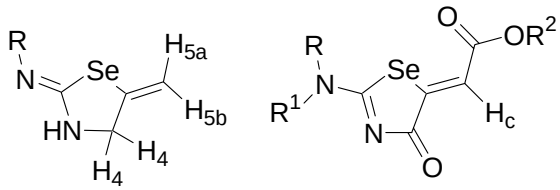


1 **4** **5**

R	R^1	Yield (%)
CH_3	CH_3	99 (**5a**)
C_2H_5	C_2H_5	96 (**5b**)
—$(CH_2)_5$—		97 (**5c**)
—$(CH_2)_2O(CH_2)_2$—		95 (**5d**)

Scheme 2

Very recently, we found very important spectral feature in the ^{1}H NMR spectra of 2-imino-5-methylidene-1,3-selenazolidine (**6**) (Figure 2).[15] The selenium shows coupling with the *trans*-proton (H_{5b} proton in **6**) exclusively, while such a coupling with the *cis*-proton (H_{5a} proton in **6**) was not observed. Our current report confirmed this important spectral feature was observed on selenium coupling $^3J(^{77}Se\text{-}^1H)$ = 10.3-11.3 Hz with the *trans*-proton in all compounds (**3a-3d** and **5a-5d**). Though we confirmed the stereochemistry of the present compounds by X-Ray diffraction in the present study, we can predict whether proton (H_c) of methylene is *cis* or *trans* configuration by using only selenium coupling in ^{1}H NMR spectra.



6 **3** or **5**

Figure 2.

Hence, we developed the synthesis method of 2-amino-4,5-dihydro-1,3-selenazol-4-one derivatives by the reactions of *N,N*-disubstituted selenoureas (**1**) with acetylene dicarboxylate without any catalyst.

EXPERIMENTAL

General

Selenoureas were synthesized according to previously described procedures.[10] The ^{77}Se chemical shifts are expressed in ppm deshielded with respect to Me_2Se in $CDCl_3$. ^3J ($^{77}Se\text{-}^1H$) values and ^1J ($^{77}Se\text{-}^{13}C$) 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 *Z*-2-Dimethylamino-5-methoxycarbonylmethylene-4,5-dihydro-1,3-selenazol-4-one (3a) Dimethyl acetylenedicarboxylate (**2**) (62 μL, 0.50 mmol) was added to a stirred solution of *N,N*-dimethylselenourea (**1a**) (75 mg, 0.50 mmol) in anhydrous ethanol (5.0 mL). The reaction mixture was stirred at room temperature for 1 h. Reaction mixture was evaporated to dryness. The residue was dissolved in acetone. Hexane was added into the mixture to precipitate **3a**. **3a** was recovered by filtration and dried. White solid (**3a**) (178 mg, Yield: 84%). mp 146-147 ºC (Acetone/Hexane), IR (KBr): 1592, 1689 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.28 (3H, s, CH_3), 3.45 (3H, s, CH_3), 3.87 (3H, s, CH_3), 7.20 (1H, s, CH, $^3J(^{77}Se\text{-}^1H)$ = 10.9 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.5 (q), 41.0 (q), 52.6 (q), 119.7 (d), 151.2 (s), 167.4 (s), 176.0 (s), 180.6 (s), ^{77}Se-NMR($CDCl_3$): δ 504.1, Anal. Calcd for $C_8H_{10}N_2O_3Se$: C, 36.80; H, 3.86; N, 10.73. Found: C, 36.56; H, 3.86; N, 10.57.

***Z*-2-Diethylamino-5-methoxycarbonylmethylene-4,5-dihydro-1,3-selenazol-4-one (3b)** Yellow solid. mp 95-96 ºC (Acetone/Hexane), IR (KBr): 1562, 1695 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 1.31 (3H, t, *J* = 7.2 Hz, CH_3), 1.39 (3H, t, *J* = 7.2 Hz, CH_3), 3.51 (2H, q, *J* = 7.2 Hz, CH_2), 3.86 (2H, q, *J* = 7.2 Hz, CH_2), 3.87 (3H, s, CH_3), 7.23 (1H, s, CH, $^3J(^{77}Se\text{-}^1H)$ = 10.9 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.9 (q), 13.8 (q), 46.2 (t), 47.5 (t), 52.6 (q), 119.6 (d), 150.9 (s), 167.6 (s), 174.5 (s), 180.8 (s), ^{77}Se NMR (95 MHz, $CDCl_3$): δ 504.0, Anal. Calcd for $C_{10}H_{14}N_2O_3Se$: C, 41.29; H, 4.88; N, 9.69. Found: C, 41.29; H, 4.86; N, 9.48.

***Z*-5-Methoxycarbonylmethylene-2-piperidino-4,5-dihydro-1,3-selenazol-4-one (3c)** Yellow crystals. mp 160-162 ºC (Acetone/Hexane), IR (KBr): 1559, 1677 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 1.69-1.82 (6H, m, CH_2), 3.49-3.54 (2H, m, CH_2), 3.86 (3H, s, CH_3), 4.04-4.08 (2H, m, CH_2), 7.22 (1H, s, CH, $^3J(^{77}Se\text{-}^1H)$ = 10.9 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.9 (t), 25.5 (t), 26.4 (t), 50.3 (q), 52.4 (t), 52.7 (t), 119.6 (d), 150.8 [^1J ($^{77}Se\text{-}^{13}C$) = 21.6 Hz] (s), 167.7 (s), 174.0 (s), 181.2 (s), ^{77}Se NMR (95 MHz, $CDCl_3$): δ 501.7, Anal. Calcd for $C_{11}H_{14}N_2O_3Se$: C, 43.86; H, 4.68; N, 9.30. Found: C, 43.81; H, 4.81; N, 9.33.

X-Ray Crystallographic Data: Single crystals were grown from acetone-hexane. Crystal system monoclinic; Space group $P2_1/a$; T = 296.2 K; a = 7.977(1) Å, b = 16.610(2) Å, c = 10.325(2) Å, β = 115.587(7)°, V = 1233.9(3) $Å^3$, Z = 4; D_c = 1.641 g/cm^3; Crystal size 0.50 x 0.30 x 0.10 mm; Limiting indices $-10 \le h \le 10$, $-21 \le k \le 13$, $-13 \le l \le 13$; Refinement method: Full-matrix least-squares on F^2, Goodness of fit on F^2: 0.86, Largest diff. peak and hole 0.82 and -0.82 e./$Å^3$; Selected bond lengths (Å) and angles (°), Se(1)-C(4): 1.881(3), C(4)-C(5): 1.517(4) Å, C(5)-N(1): 1.357(4) Å, N(1)-C(6): 1.311(4) Å, C(6)-Se(1): 1.937(3) Å, C(6)-N(2): 1.314(4) Å, C(4)-C(3): 1.329(4) Å, C(6)-Se(1)-C(4): 83.6(1)°, Se(1)-C(4)-C(5): 109.8(2)°, C(4)-C(5)-N(1): 115.5(3)°, C(5)-N(1)-C(6): 113.8(3)°, N(1)-C(6)-Se(1): 117.3(2)° for all data.[13]

***Z*-5-Methoxycarbonylmethylene-2-morpholino-4,5-dihydro-1,3-selenazol-4-one (3d)** Yellow solid. mp 201-202 ºC (Acetone/Hexane), IR (KBr): 1550, 1690 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 3.58 (2H, t, *J* = 4.9 Hz, CH_2), 3.81 (2H, t, *J* = 4.9 Hz, CH_2), 3.86 (2H, t, *J* = 4.9 Hz, CH_2), 3.87 (3H, s, CH_3), 4.13 (2H, t, *J* = 4.9 Hz, CH_2), 7.24 (1H, s, CH, $^3J(^{77}Se\text{-}^1H)$ = 11.3 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 49.3 (t), 50.6 (q), 52.7 (t), 66.2 (t), 66.3 (t), 120.2 (d), 149.9 (s), 167.5 (s), 175.3 (s), 180.8 (s), ^{77}Se NMR (95 MHz, $CDCl_3$): δ 503.1, Anal. Calcd for $C_{10}H_{12}N_3O_4Se$: C, 39.62; H, 3.99; N, 9.24. Found: C, 39.31; H, 4.02; N, 9.10.

***Z*-5-Carboxylmethylene-2-dimethylamino-4,5-dihydro-1,3-selenazol-4-one (5a)** Yellow solid. mp 272-274 ºC, IR (KBr): 1563, 1693, 3459 cm^{-1}, ^1H NMR (500 MHz, DMSO-*d*6): δ 2.98 (3H, s, CH_3), 3.05 (3H, s, CH_3), 6.67 (1H, s, CH, $^3J(^{77}Se\text{-}^1H)$ = 10.9 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.2 (q), 41.1 (q),

119.9 (d), 151.4 (s), 167.7 (s), 175.2 (s), 179.6 (s), ^{77}Se-NMR (DMSO-*d*6): δ 494.9, Anal. Calcd for $C_7H_8N_2O_3Se$: C, 34.02; H, 3.26; N, 11.34. Found: C, 33.87; H, 3.42; N, 11.11.

***Z*-5-Carboxylmethylene-2-diethylamino-4,5-dihydro-1,3-selenazol-4-one (5b)** Pink Solid. mp 168-169 ºC, IR (KBr): 1550, 1685, 3454 cm^{-1}, ^{1}H NMR (500 MHz, CD_3OD): δ 1.28 (3H, t, *J* = 7.2 Hz, CH_3), 1.35 (3H, t, *J* = 7.2 Hz, CH_3), 3.58 (2H, q, *J* = 7.2 Hz, CH_2), 3.82 (2H, q, *J* = 7.2 Hz, CH_2), 7.09 (1H, s, CH, $^3J(^{77}Se\text{-}^1H)$ = 10.9 Hz), ^{13}C NMR (125 MHz, CD_3OD): δ 13.2 (q), 14.1 (q), 47.5 (t), 49.2 (t), 121.8 (d), 151.3 (s), 169.3 (s), 177.0 (s), 183.0 (s), ^{77}Se NMR (95 MHz, CD_3OD): δ 500.6, Anal. Calcd for $C_9H_{12}N_2O_3Se$: C, 39.28; H, 4.40; N, 10.18. Found: C, 38.92; H, 4.41; N, 9.86.

***Z*-5-Carboxylmethylene-2-piperidino-4,5-dihydro-1,3-selenazol-4-one (5c)** White solid. mp 194-196 ºC, IR (KBr): 1540, 1686, 3440 cm^{-1}, ^{1}H NMR (500 MHz, CD_3OD): δ 1.68-1.82 (6H, m, CH_2), 3.56-3.63 (2H, m, CH_2), 3.98-4.04 (2H, m, CH_2), 7.09 (1H, s, CH, $^3J(^{77}Se\text{-}^1H)$ = 10.3 Hz), ^{13}C NMR (125 MHz, CD_3OD): δ 24.9 (t), 26.8 (t), 27.6 (t), 51.3 (t), 53.9 (t), 121.5 (d), 151.4 (s), 169.3 (s), 176.3 (s), 183.4 (s), ^{77}Se NMR (95 MHz, $CDCl_3$): δ 498.9, Anal. Calcd for $C_{10}H_{12}N_2O_3Se$: C, 41.82; H, 4.21; N, 9.75. Found: C, 42.21; H, 4.37; N, 9.64.

***Z*-5-Carboxylmethylene-2-morpholino-4,5-dihydro-1,3-selenazol-4-one (5d)** Yellow solid. mp 259-260 ºC, IR (KBr): 1549, 1641, 3441 cm^{-1}, ^{1}H NMR (500 MHz, DMSO-*d*6): δ 3.62 (2H, t, *J* = 4.9 Hz, CH_2), 3.69 (2H, t, *J* = 4.9 Hz, CH_2), 3.72 (2H, t, *J* = 4.9 Hz, CH_2), 3.95 (2H, t, *J* = 4.9 Hz, CH_2), 6.95 (1H, s, CH, $^3J(^{77}Se\text{-}^1H)$ = 10.3 Hz), ^{13}C NMR (125 MHz, DMSO-*d*6): δ 49.0 (t), 50.6 (t), 65.6 (t), 65.9 (t), 120.0 (d), 150.2 (s), 167.7 (s), 174.6 (s), 180.0 (s), ^{77}Se NMR (95 MHz, DMSO-*d*6): δ 497.3, Anal. Calcd for $C_9H_{10}N_2O_3Se$: C, 37.38; H, 3.49; N, 9.69. Found: C, 37.38; H, 3.56; N, 9.47.

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