SYNTHESIS OF 2-AMINO-1,3-SELENAZOLES BY REACTION OF $N,N$-UNSUBSTITUTED SELENoureAS WITH $\alpha,\beta$-UNSATURATED ALDEHYDES

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

INTRODUCTION

There are many 1,3-selenazoles found in the literatures.\textsuperscript{1} Many of them are studied as potential pharmaceutical and dye agents.\textsuperscript{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.\textsuperscript{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 $\alpha$-haloketones,\textsuperscript{4} chloroacetoniitrile\textsuperscript{5} and $\alpha$-haloacyl halides\textsuperscript{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.\textsuperscript{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 \(\alpha,\beta\)-unsaturated aldehydes in alcohol.

RESULTS AND DISCUSSION

\[
\begin{align*}
\text{Selenourea (1)} & \quad + \quad \text{\(\alpha,\beta\)-Unsaturated Aldehyde (2)} \quad \xrightarrow{\text{FeCl}_3, \text{EtOH, 2 h, rt}} \quad \text{2-Amino-1,3-selenazole (3)} \\
\begin{array}{c}
\text{Reaction Scheme 1} \\
\text{Table 1. Synthesis of 2-Amino-1,3-selenazoles (3)}
\end{array}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Selenourea (1)</th>
<th>(\alpha,\beta)-Unsaturated Aldehyde (2)</th>
<th>2-Amino-1,3-selenazole (3)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1a)</td>
<td>(2a)</td>
<td>(3a)</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>(1b)</td>
<td>(2a)</td>
<td>(3b)</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>(1c)</td>
<td>(2a)</td>
<td>(3c)</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>(1d)</td>
<td>(2a)</td>
<td>(3d)</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>(1d)</td>
<td>(2b)</td>
<td>(3e)</td>
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<tr>
<td>6</td>
<td>(1d)</td>
<td>(2c)</td>
<td>(3f)</td>
<td>26</td>
</tr>
<tr>
<td>7</td>
<td>(1d)</td>
<td>(2d)</td>
<td>(3g)</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>(1d)</td>
<td>(2e)</td>
<td>(3h)</td>
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\(\text{a} \) 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-selenazoles in high yields. 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. 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.

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. The $^{77}$Se chemical shifts are expressed in ppm deshielded with respect to Me$_2$Se 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.

![Scheme 2](image-url)
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 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 (79.2 mg, 68 %) as yellow liquid. IR (neat): 2868, 1555 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.20 (3H, t, J = 6.9 Hz, CH₃), 3.08 (6H, s, CH₃), 3.50 (2H, q, J = 6.9 Hz, CH₂), 4.55 (2H, s, CH₂, ³J(⁷⁷Se-¹H) = 9.7 Hz), 6.99 (1H, s, CH); ¹³C NMR (125 MHz, CDCl₃): δ 15.0, 40.9, 64.4, 67.1, 128.8, 139.6, 174.8; ⁷⁷Se NMR (95 MHz, CDCl₃): δ 542.7; Anal. Calcd for C₈H₁₄N₂OSe: 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, CDCl₃): δ 1.21 (3H, t, J = 6.9 Hz, CH₃), 1.23 (6H, t, J = 6.9 Hz, CH₃), 3.45 (4H, q, J = 6.9 Hz, CH₂), 4.55 (2H, s, CH₂, ³J(⁷⁷Se-¹H) = 9.7 Hz), 6.99 (1H, s, CH); ¹³C NMR (125 MHz, CDCl₃): δ 12.5, 15.0, 46.4, 64.4, 67.1, 127.2, 139.4, 173.1; ⁷⁷Se NMR (95 MHz, CDCl₃): δ 538.9; Anal. Calcd for C₁₀H₁₈N₂OSe: 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, CDCl₃): δ 1.13 (3H, t, J = 6.9 Hz, CH₃), 3.37 (4H, t, J = 5.2 Hz, CH₂), 3.43 (2H, q, J = 6.9 Hz, CH₂), 4.49 (2H, s, CH₂, ³J(⁷⁷Se-¹H) = 9.7 Hz), 6.93 (1H, s, CH); ¹³C NMR (125 MHz, CDCl₃): δ 15.1, 49.4, 64.6, 66.1, 67.0, 130.3, 139.0, 175.7; ⁷⁷Se NMR (95 MHz, CDCl₃): δ 553.5; Anal. Calcd for C₁₀H₁₆N₂O₂Se: 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, CDCl₃): δ 1.20 (3H, t, J = 6.9 Hz, CH₃), 1.61-1.70 (6H, m, CH₂), 3.40-3.46 (4H, m, CH₂) 3.50 (2H, q, J = 6.9 Hz, CH₂), 4.56 (2H, s, CH₂, ³J(⁷⁷Se-¹H) = 9.7 Hz), 6.95 (1H, s, CH); ¹³C NMR (125 MHz, CDCl₃): δ 15.1, 24.2, 25.1, 50.7, 64.5, 67.2, 128.6 [¹J(⁷⁷Se-¹³C) = 93.5 Hz], 139.3, 175.5; ⁷⁷Se NMR (95 MHz, CDCl₃): δ 545.6; Anal. Calcd for C₁₁H₁₈N₂O₂Se: C, 43.64; H, 6.58; N, 10.18. Found: C, 43.44; H, 6.09; N, 10.15.

5-(1-Ethoxyethyl)-2-piperidino-1,3-selenazole (3e) White solid. mp 54–56 °C; IR (KBr): 2932, 1531 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.17 (3H, t, J = 6.9 Hz, CH₃), 1.49 (3H, d, J = 6.3 Hz, CH₃), 1.61-1.70 (6H, m, CH₂), 3.32-3.38 (1H, m, CH₂), 3.40-3.46 (4H, m, CH₂), 3.47-3.53 (1H, m, CH₂), 4.48 (1H, q, J = 6.3 Hz, CH), 6.92 (1H, s, CH); ¹³C NMR (125 MHz, CDCl₃): 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\(_3\)): \(\delta\) 522.1; Anal. Caled for C\(_{13}\)H\(_{20}\)N\(_2\)OSe: 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 °C; IR (KBr): 2932, 1526 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 522.5; Anal. Calcd for C\(_{13}\)H\(_{22}\)N\(_2\)OSe: 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\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 539.1; Anal. Calcd for C\(_{13}\)H\(_{22}\)N\(_2\)OSe: 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\(_3\)): \(\delta\) 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\(_2\)), \(^3\)J (\(^{77}\)Se-\(^1\)H) = 11.2 Hz), 6.97 (1H, s, CH); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 24.1, 25.1, 50.6, 56.8, 69.0, 127.9, 139.6, 175.5; \(^{77}\)Se NMR (95 MHz, CDCl\(_3\)): \(\delta\) 544.3; Anal. Calcd for C\(_{10}\)H\(_{16}\)N\(_2\)OSe: 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, 1526 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.17 (6H, d, \(J = 6.3\) Hz, CH\(_3\)), 3.22 (3H, s, CH\(_3\)), 3.42-3.48 (4H, m, CH\(_2\)), 4.56 (2H, s, CH\(_2\)), \(^3\)J (\(^{77}\)Se-\(^1\)H) = 11.2 Hz), 6.97 (1H, s, CH); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 22.0, 24.2, 25.1, 50.7, 64.6, 69.5, 129.4, 138.8, 175.4; \(^{77}\)Se NMR (95 MHz, CDCl\(_3\)): \(\delta\) 546.9; Anal. Calcd for C\(_{12}\)H\(_{20}\)N\(_2\)OSe: 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 °C; IR (KBr): 2934, 1526 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.25 (9H, s, CH\(_3\)), 1.62-1.67 (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\(_2\)), \(^3\)J (\(^{77}\)Se-\(^1\)H) = 9.2 Hz), 6.94 (1H, s, CH); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 22.0, 24.2, 25.1, 50.7, 64.6, 69.5, 129.4, 138.8, 175.4; \(^{77}\)Se NMR (95 MHz, CDCl\(_3\)): \(\delta\) 546.9; Anal. Calcd for C\(_{13}\)H\(_{22}\)N\(_2\)OSe: C, 51.17; H, 7.02; N, 9.75. Found: C, 51.96; H, 7.59; N, 9.18.

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. 15550030 and 17550099) to which we are grateful.
REFERENCES


