Facile synthesis of novel functionalized 1,3-selenazoles

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Abstract
The reaction of selenourea with diethyl 2,4-dibromo-3-oxoglutarate afforded ethyl 2-(2-amino-5-ethoxycarbonyl-1,3-selenazol-4-yl)-2-bromoethanoate. Treatment of the latter with acylating agents and various nucleophiles gave a series of new 4,5-disubstituted 2-amino-1,3-selenazoles. All compounds were characterized spectroscopically. The crystal structure determination of ethyl 2-(2-amino-5-ethoxycarbonyl-1,3-selenazol-4-yl)-2-bromoethanoate is reported.

Keywords: 2-Amino-1,3-selenazole, selenourea, Hantzsch reaction, heterocycles

Introduction
Considerable interest in the synthesis of 1,3-selenazole derivatives exists due to their potential for practical applications. Functionalized 1,3-selenazole moieties are present in many pharmacologically active substances. The prominent examples are a potent antiviral agent selenazofurin (2-β-ribofuranosyl-1,3-selenazole-4-carboxamide) 1, 2 and a histamine H₂-agonist amselamine [2-amino-5-(2-aminoethyl)-4-methyl-1,3-selenazole] 2. 3 N-Acylated 2-amino-4-(isothiocyanatomethyl)-1,3-selenazoles (3) and the corresponding 2-carbamates possess antitumoral activity. 4 Recently, it was reported that 2-piperidino- and 4-phenyl-2-piperidino-1,3-selenazoles exhibit strong superoxide anion-scavenging activity, while 2-piperidino- and 2-morpholino-5-chloroacetyl-1,3-selenazoles (4a, b) show antioxidant activity and strongly inhibit lipopolysaccharide-induced nitric oxide release from microglial cells. 6 Moreover, 2-amino-1,3-selenazole derivatives found application in the synthesis of organic dyes. 7

![Image of some biologically active 1,3-selenazole derivatives.](image-url)
In view of the importance of substituted 1,3-selenazoles, several methods for their preparation have been reported. The 2-amino-1,3-selenazoles are generally prepared via the [3+2] route using the Hantzsch method, which is based on the reaction of selenoureas with α-halogenated carbonyl compounds. The latter starting materials can be easily obtained by chlorination or bromination of aliphatic ketones or other similar carbonyl derivatives. The reaction of selenourea with α-halogenated carbonyl compounds gives a variety of 2-amino-1,3-selenazoles, bearing substituents at 4- and 5-positions of the heterocyclic ring. For example, treatment of selenourea with 1,3-dichloroacetone and phenylacetyl bromide afforded 4-chloromethyl- and 4-phenyl-2-amino-1,3-selenazole, respectively, while the reaction with ethyl α-bromoacetooacetate gave ethyl 2-amino-4-methyl-1,3-selenazole-5-carboxylate.

Recently, we showed that diethyl 2,4-dibromo-3-oxoglutarate can serve as a suitable synthon for the preparation of highly functionalized 2-aminothiazole derivatives. In an effort to broaden the scope of this reagent in the Hantszch synthesis and to further development of methods for preparation of functionalized 1,3-selenazole derivatives, the objective of this work is to investigate the reaction of diethyl 2,4-dibromo-3-oxoglutarate with selenourea and to study the structure and chemical transformations of the obtained novel cyclic products.

**Results and Discussion**

Dibromination of diethyl 3-oxoglutarate 1 with NBS in carbon tetrachloride produced diethyl 2,4-dibromo-3-oxoglutarate 2 as a mixture of diastereomers, which was directly used in the next reaction step. The reaction of dibrominated carbonyl compound 2 with selenourea was carried out under argon in ethanol at room temperature for 48 h. Then the reaction mixture was treated with a base and the separated material was extracted with an organic solvent. The purification of the crude product by flash chromatography gave ethyl 2-(2-amino-5-ethoxycarbonyl-1,3-selenazol-4-yl)-2-bromoethanoate (3) in 61% yield (Scheme 1).

![Scheme 1](image-url)

The structure assignment of 3 was based on spectral data. The IR spectrum shows a broad band at 3151 cm⁻¹ for NH₂ and sharp bands at 1737 and 1718 cm⁻¹, which are due to diester C=O groups. The ¹H NMR spectrum contains the characteristic methine proton (CHBr) signal at 6.52 ppm. The
$^{13}$C NMR spectrum of 3 shows the characteristic signals of the 1,3-selenazole ring skeleton carbons at 113.2, 155.3 and 162.7 ppm, while a signal of the methine carbon (CHBr) is situated at 42.2 ppm.

The single crystal X-ray structure (Figure 2)$^{13}$ shows that the skeleton of the asymmetric unit contains five-membered 1,3-selenazole ring, with bromo(ethoxycarbonyl)methyl group attached to the atom C(4) and ethoxycarbonyl group attached to the atom C(5). The C(2)-Se and C(5)-Se bond lengths in the molecule 3 are 1.898(4) and 1.881(15) Å, respectively, and they are similar to that found in related structures.$^{6,14}$ The bond angle C(2)-Se-C(5) is 84.3(6)$^\circ$.

![Figure 2. ORTEP drawing of functionalized 2-amino-1,3-selenazole 3.](image)

In order to evaluate the synthetic utility of 2-amino-1,3-selenazole 3 acylation reactions of the amino group have been investigated. 2-Amino-1,3-selenazole 3 was subjected to acetylation with acetic anhydride in the presence of DMAP to give the amide 4a. The IR spectrum of 4a contains the primary amide bands at $\nu_{\text{N-H}} = 3159$ and $\nu_{\text{C=O}} = 1659$ cm$^{-1}$, while the $^1$H NMR spectrum shows a singlet of the acetyl group protons at 2.20 ppm. Treatment of the amine 3 with Boc$_2$O in the presence of DMAP gave the N-Boc protected product 4b. The $^1$H NMR spectrum of 4b contains a singlet of the tert-butoxy group at 1.48 ppm. Next, we investigated representative nucleophilic substitution reactions of compound 3 with KSCN, NaN$_3$, amines and thiols. The nucleophilic displacement of a bromide at the saturated carbon with the thiocyanate group gave a substituted product 5. The IR spectrum of 5 showed a sharp band at 2158 cm$^{-1}$ assigned to the thiocyanate group.$^{15}$ In its $^{13}$C NMR spectrum, the characteristic resonance signal of the thiocyanate carbon appeared at 103.6 ppm.

Treatment of 3 with sodium azide in DMSO at 60 °C for 6 h, followed by work-up consisting of dilution with dichloromethane, washing the organic layer with water and concentration under reduced pressure, gave the azido derivative 6. The absorption band at 2122 cm$^{-1}$, which is due to the azido group,$^{15}$ is observed in the IR spectrum of 6.

Then we turned our attention to study the possibility of substitution of a bromide by an amino group. The reaction of the bromide 3 with methyl amine hydrochloride in ethanol in the presence of bases, led to the formation of the secondary amine 7a. The IR spectra of 7a showed broad bands in the area 3324 – 3180 cm$^{-1}$ for the NH$_2$ and NH groups and the intense bands at 1738 and 1696 cm$^{-1}$.
assigned to the carbonyl groups of the diester. When compound 3 was reacted with benzylamine, the secondary amine 7b was obtained in 62% yield.

![Scheme 2](image)

**Scheme 2.** Reagents and conditions: i, Ac₂O, DMAP, DCM, reflux, 6 h, or Boc₂O, DMAP, DCM, reflux, 4 h; ii, KSCN, acetone, rt, 48 h; iii, NaN₃, DMSO, 60 °C, 6 h; iv, MeNH₂·HCl or BnNH₂, K₂CO₃, TEA, EtOH, rt, 5 days; v, EtSH, TEA, EtOH, rt, 5 days; vi, EtSH, TEA, EtOH, rt, 5 days; vii, Ac₂O, DMAP, DCM, reflux, 6 h.

To assess further its reactivity, compound 3 was treated with thiols. However, the reaction of the bromide 3 with ethanethiol in the presence of TEA did not give the desired sulfide, instead debrominated compound 8 was obtained. The reaction with methyl thioglycolate in similar conditions afforded the same product 8. The ¹H NMR spectrum of 8 revealed a singlet at 3.85 ppm for methylene protons (CH₂CO). ¹³C NMR spectrum showed the presence of three methylene carbons at 36.6 (CH₂CO), 60.0 (OCH₂), 60.1 (OCH₂), respectively. Similarly, treatment of 2-acetylamino-1,3-selenazole 4a with ethanethiol afforded the corresponding debrominated compound 9. The latter compound was also obtained by reaction of 8 with acetic anhydride in the presence of DMAP.

The use of thiols as catalysts and hydrogen donors for radical chain reduction of organic halides is well documented in the literature. For example, 1,2,2,6,6-pentamethylpiperidine/mercaptoethanol system was shown to be an effective reducing agent for the radical chain reduction of bromoesters. Therefore, it can be assumed, that ethanethiol/TEA or methyl thioglycolate/TEA systems possess similar reductive properties and accomplish dehalogenation of bromoesters 3 and 4a by a radical-chain mechanism.
Conclusions

In summary, an efficient route for the preparation of a wide variety of highly functionalized 1,3-selenazoles has been developed. This method allows functionalized 1,3-selenazoles to be easily available for further investigations into their chemical and biological properties.

Experimental Section

General. Melting points were determined in open capillary tubes with a Büchi B-540 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum One spectrometer using potassium bromide pellets. $^1$H NMR spectra were recorded at 300 MHz on a Varian Unity Inova spectrometer. $^{13}$C NMR spectra were registered at 75 MHz using the instrument mentioned above. Chemical shifts, expressed in ppm, were relative to tetramethylsilane (TMS). Mass spectra were measured using Waters ZQ 2000 instrument (ion spray). Diffraction data were collected on Bruker-Nonius KappaCCD diffractometer at room temperature and also at –100 °C. The crystal structures were solved using known programs. Elemental analyses were performed by the Microanalytical Laboratory, Department of Organic Chemistry, Kaunas University of Technology, Lithuania. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254) were used.

Ethyl 2-(2-amino-5-ethoxycarbonyl-1,3-selenazol-4-yl)-2-bromoethanoate (3). To a solution of selenourea (1.60 g, 13 mmol) in absolute ethanol (50 mL) 2,4-dibromo-3-oxoglutarate (4.68 g, 13 mmol) was added dropwise and the mixture was stirred under argon at rt for 48 h. The solvent was removed at reduced pressure and the residue was dissolved in 100 mL of water. The pH was then adjusted to pH 9 with sat. Na$_2$CO$_3$ and the aqueous solution was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel (hexane – ethyl acetate, 4 : 1) to afford the title compound 3 as pale yellow crystals (3.05 g, 61%), mp 179-180 °C (from ethanol). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ (ppm) 1.15 (3H, t, $J = 7.1$ Hz, CH$_3$), 1.23 (3H, t, $J = 7.1$ Hz, CH$_3$), 4.14 (2H, q, $J = 7.1$ Hz, CH$_2$), 4.19 (2H, q, $J = 7.1$ Hz, CH$_2$), 6.52 (1H, s, CH), 8.32 (2H, br s, NH$_2$). $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ (ppm) 13.9 (CH$_3$), 14.2 (CH$_3$), 42.2 (CH), 60.7 (CH$_2$), 62.2 (CH$_2$) 113.2 (C-5), 155.3 (C-4), 162.7 (C-2), 165.6 (C=O), 172.4 (C=O). MS m/z (%): 383/85 (M$^+$, 42/74). Anal. Calcd for C$_{10}$H$_{13}$BrN$_2$O$_4$Se: C 31.27; H 3.41; N 7.29. Found: C 31.67; H 3.53; N 7.17.

Ethyl 2-(2-acetylamino-5-ethoxycarbonyl-1,3-selenazol-4-yl)-2-bromoethanoate (4a). To a precooled in an ice bath solution of 2-amino-1,3-selenazole 3 (300 mg, 0.78 mmol)) and DMAP (125 mg, 1.02 mmol) in dry dichloromethane (8 mL) a solution of acetic anhydride (150 mg, 0.14 mL, 1.5 mmol) in dichloromethane (2 mL) was added dropwise. The reaction mixture was allowed to reach rt and stirred under argon for 6 h, then washed with brine and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue material was subjected to
flash chromatography with silica gel using a solvent gradient (from 20 to 50% ethyl acetate in hexane) to give the title compound 4a as white crystals (240 mg, 72%), mp 120-121 °C (from ethyl acetate – hexane). $^1$H NMR (300 MHz, DMSO-d$_6$): δ (ppm) 1.14 (3H, t, $J$ = 7.1 Hz, CH$_2$CH$_3$), 1.29 (3H, t, $J$ = 7.1 Hz, CH$_2$CH$_3$), 2.20 (3H, s, COCH$_3$), 4.16 (2H, q, $J$ = 7.1 Hz, CH$_2$), 4.27 (2H, q, $J$ = 7.1, CH$_2$), 6.66 (1H, s, CH), 13.12 (1H, br s, NH). $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ (ppm) 13.9 (CH$_2$CH$_3$), 14.0 (CH$_2$CH$_3$), 22.2 (COCH$_3$), 42.2 (CH), 61.3 (CH$_2$), 62.4 (CH$_2$), 120.8 (C-5), 152.6 (C-4), 162.5, 162.9 (C-2 and C=O), 165.7 (C=O), 170.3 (C=O). IR (KBr, cm$^{-1}$): $\nu$ N-H = 3159; $\nu$ C=O = 1762; v$_{C=O}$ = 1640. Anal. Calcd for C$_7$H$_7$BrN$_2$O$_3$Se: C 33.82; H 3.62; N 13.57. Found: C 33.84; H 3.74; N 13.60.

**Ethyl 2-(2-tert-butoxycarbonylamino-5-ethoxycarbonyl-1,3-selenazol-4-yl)-2-bromoethanoate (4b)** was obtained similarly to 4a from 3 (300 mg, 0.78 mmol) and Boc$_2$O (200 mg, 0.94 mmol) in 210 mg yield (55%) with mp 124-125 °C (ethyl acetate - hexane). $^1$H NMR (300 MHz, DMSO-d$_6$): δ (ppm) 1.14 (3H, t, $J$ = 7.1, CH$_2$CH$_3$), 1.28 (3H, t, $J$ = 7.1, CH$_2$CH$_3$), 1.48 (9H, s, 3xCH$_3$), 4.13 (2H, q, $J$ = 7.1, CH$_2$), 4.28 (2H, q, $J$ = 7.1, CH$_2$), 6.62 (1H, s, CH), 12.50 (1H, br s, NH). $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ (ppm) 13.8 (CH$_2$CH$_3$), 13.9 (CH$_2$CH$_3$), 27.7 [3C, (CH$_3$)$_3$], 42.2 (CH), 61.3 (CH$_2$), 62.4 (CH$_2$), 82.6 [C(CH$_3$)$_3$], 120.6 (C-5), 153.2, 153.5, 162.7, 165.0, 165.5. IR (KBr, cm$^{-1}$): $\nu$ N-H = 3256; $\nu$ C=O = 1762; v$_{C=O}$ = 1720; v$_{C=O}$ = 1679. MS m/z (%): 507/509 (M + H$^+$, Na; 52/42). Anal. Calcd for C$_{15}$H$_{23}$BrN$_2$O$_3$Se: C 37.12; H 4.73; N 11.60. Found: C 37.14; H 4.73; N 11.65.

**Ethyl 2-(2-amino-5-ethoxycarbonyl-1,3-selenazol-4-yl)-2-thiocyanatoethanoate (5).** To a solution of 2-amino-1,3-selenazole 3 (300 mg, 0.78 mmol) in dry acetone (10 mL) KSCN (91 mg, 0.94 mmol) was added and the reaction mixture was stirred under argon at rt for 48 h. Then it was concentrated under reduced pressure. The resulting residue was diluted with dichloromethane (15 mL) and the solid was removed by filtration. The solvent was evaporated under reduced pressure and the residue subjected to flash chromatography with silica gel (hexane - ethyl acetate, 3 : 1) to give the title compound 5 as white crystals (110 mg, 58%), mp 152-153 °C (from ethyl acetate - hexane). $^1$H NMR (300 MHz, DMSO-d$_6$): δ (ppm) 1.16 (3H, t, $J$ = 7.2 Hz, CH$_3$), 1.23 (3H, t, $J$ = 7.2, CH$_3$), 4.16 (2H, q, $J$ = 7.2 Hz, CH$_2$), 4.17 (2H, q, $J$ = 7.2 Hz, CH$_2$), 6.12 (1H, s, CH), 8.16 (2H, br s, NH$_2$). $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ (ppm) 13.8 (CH$_3$), 14.1 (CH$_3$), 43.7 (CH), 60.6 (CH$_2$), 62.2 (CH$_2$), 103.6 (SCN), 109.8 (C-5), 152.2 (C-4), 161.0, 168.0 (C-2 and C=O), 170.4 (C=O). IR (KBr, cm$^{-1}$): $\nu$ N-H = 3389; $\nu$ N-H = 3282; $\nu$ SCN = 2158; v$_{C=O}$ = 1721; v$_{C=O}$ = 1691. MS m/z (%): 362 (M$^+$, 12). Anal. Calcd for C$_{13}$H$_{13}$N$_3$O$_4$SSe: C 36.47; H 3.32; N 11.60. Found: C 36.38; H 4.01; N 11.55.

**Ethyl 2-(2-amino-5-ethoxycarbonyl-1,3-selenazol-4-yl)-2-azidoethanoate (6).** To a solution of 2-amino-1,3-selenazole 3 (0.5 g, 1.30 mmol) in dry DMSO (8 mL) sodium azide (90 mg, 1.40 mmol) was added. The mixture was heated with stirring under argon at 60 °C for 6 h, then the resulting solution was allowed to reach rt and diluted with dichloromethane (50 mL). The organic solution was washed with brine (3 x 20 mL) and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue material was subjected to flash chromatography with silica gel using a solvent gradient (from 25 to 50% ethyl acetate in hexane) to give the title compound 6 as white crystals (190 mg, 42%), mp 163-164 °C (dichloromethane). $^1$H NMR (300 MHz, DMSO-d$_6$): δ (ppm) 1.15 (3H, t, $J$ = 7.2 Hz, CH$_3$), 1.22 (3H, t, $J$ = 7.2 Hz, CH$_3$), 4.11-4.21 (4H, m, 2xCH$_2$), 4.17 (2H, q, $J$ = 7.2 Hz, CH$_2$), 6.66 (1H, s, CH), 13.12 (1H, br s, NH). $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ (ppm) 13.8 (CH$_3$), 14.1 (CH$_3$), 43.7 (CH), 60.6 (CH$_2$), 62.2 (CH$_2$), 103.6 (SCN), 109.8 (C-5), 152.2 (C-4), 161.0, 168.0 (C-2 and C=O), 170.4 (C=O). IR (KBr, cm$^{-1}$): $\nu$ N-H = 3389; $\nu$ N-H = 3282; $\nu$ SCN = 2158; v$_{C=O}$ = 1721; v$_{C=O}$ = 1691. MS m/z (%): 362 (M$^+$, 12). Anal. Calcd for C$_{13}$H$_{13}$N$_3$O$_4$SSe: C 36.47; H 3.62; N 11.55. Found: C 36.38; H 4.01; N 11.55.
5.76 (1H, s, CH), 8.33 (2H, br s, NH$_2$). $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ (ppm) 13.9 (CH$_3$), 14.1 (CH$_3$), 57.5 (CH), 60.6 (CH$_2$), 61.6 (CH$_2$), 113.8 (C-5), 154.1 (C-4), 162.8, 167.6 (C-2 and C=O), 173.1 (C=C=O). IR (KBr, cm$^{-1}$): $\nu_{N-H}$ = 3407; $\nu_{N-H}$ = 3290; $\nu_a$zide = 2122; $\nu_{C=O}$ = 1744; $\nu_{C=O}$ = 1696. MS m/z (%): 370 (M + H$^+$, Na; 58). Anal. Calcd for C$_{10}$H$_13$N$_2$Se: C 34.69; H 3.78%; N 20.23. Found: C 34.75; H 3.98; N 19.90.

**Ethyl 2-(2-amino-5-ethoxycarbonyl-1,3-selenazol-4-yl)-2-methylaminoethanoate (7a).** To a solution of 2-amino-1,3-selenazole 3 (0.3 g, 0.78 mmol) in absolute ethanol (8 mL) K$_2$CO$_3$ (0.14 g, 1.0 mmol), triethylamine (0.2 g, 0.25 mL, 2.0 mmol) and methylamine hydrochloride (0.1 g, 1.48 mmol) were added. The mixture was stirred under argon at rt for 5 days. The solvent was removed under reduced pressure, water (15 mL) was added to the residue and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was twice recrystallized from dichloromethane to afford the title compound 7a as white crystals (133 mg, 51%), mp 176-177 °C. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ (ppm) 1.11 (3H, t, $J$ = 7.2 Hz, CH$_2$CH$_3$), 1.22 (3H, t, $J$ = 7.2 Hz, CH$_2$CH$_3$), 2.21 (3H, s, NCH$_3$), 4.05 (2H, q, $J$ = 7.2 Hz, CH$_2$CH$_3$), 4.14 (2H, q, $J$ = 7.2 Hz, CH$_2$CH$_3$), 5.15 (1H, s, CH), 8.21 (2H, br s, NH$_2$). $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ (ppm) 14.1 (CH$_2$CH$_3$), 14.2 (CH$_2$CH$_3$), 33.56 (NCH$_3$), 45.30 (CH), 60.2 (CH$_3$), 60.3 (CH$_2$), 112.8 (C-5), 158.8 (C-4), 163.1, 170.5 (C-2 and C=O), 172.8 (C=O). IR (KBr, cm$^{-1}$): $\nu_{N-H}$ = 3324; $\nu_{N-H}$ = 3180; $\nu_{C=O}$ = 1744; $\nu_{C=O}$ = 1696. MS m/z (%): 334 (M$^+$, 20), 358 (M + H$^+$, Na; 36). Anal. Calcd for C$_{11}$H$_{17}$N$_2$O$_2$Se: C 49.83; H 5.43; N 10.24. Found: C 49.83; H 5.37; N 10.24.

**Ethyl 2-(2-amino-5-ethoxycarbonyl-1,3-selenazol-4-yl)-2-benzylaminoethanoate (7b).** was obtained similarly to 7a from 3 (0.3 g, 0.78 mmol) and benzylamine (167 mg, 1.56 mmol) in 158 mg yield (62%) with mp 168-169 °C (dichloromethane). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ (ppm) 1.11 (3H, t, $J$ = 6.9 Hz, CH$_2$CH$_3$), 1.15 (3H, t, $J$ = 6.9 Hz, CH$_3$), 2.45 (1H, br s, NH), 3.63 (2H, s, NCH$_2$), 4.00-4.15 (4H, m, 2xOCH$_2$), 5.27 (1H, s, CH), 7.28-7.30 (5H, m, ArH), 8.17 (2H, br s, NH$_2$). $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ (ppm) 14.0 (CH$_3$), 14.1 (CH$_3$), 50.0, 58.0, 60.1, 60.2, 113.0, 126.7, 127.8 (2C), 128.1 (2C), 140.0, 158.7, 162.9, 170.6, 172.6. IR (KBr, cm$^{-1}$): $\nu_{N-H}$ = 3303; $\nu_{C-O}$ = 3104; $\nu_{C=O}$ = 1731; $\nu_{C=O}$ = 1689. MS m/z (%): 434 (M$^+$, 20), 358 (M + H$^+$, Na; 36). Anal. Calcd for C$_{19}$H$_{24}$N$_2$O$_2$Se: C 49.76; H 5.16; N 10.24. Found: C 49.59; H 7.2; N 9.78.

**Ethyl 2-(2-amino-5-ethoxycarbonyl-1,3-selenazol-4-yl)ethanoate (8).** To solution of 2-amino-1,3-selenazole 3 (0.3 g, 0.78 mmol) and triethyl amine (0.15 g, 0.2 mL, 1.48 mmol) in absolute ethanol (8 mL) ethanethiol (0.24 g, 0.28 mL, 3.9 mmol) was added dropwise and the reaction mixture was stirred under argon at rt for 5 days. The solvent was evaporated under reduced pressure, the resulting residue was diluted with dichloromethane (10 mL) and the solid was removed by filtration. The organic extract was washed with brine and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue material was subjected to flash chromatography with silica gel using a solvent gradient (from 20 to 50% ethyl acetate in hexane) to give the title compound 8 as white crystals (144 mg, 60%), mp 124-125 °C (ethyl acetate – hexane). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ (ppm) 1.37 (3H, t, $J$ = 7.2 Hz, CH$_3$), 1.20 (3H, t, $J$ = 7.2 Hz, CH$_3$), 3.85 (2H, s, CH$_2$CO), 4.05 (2H, q, $J$ = 7.2 Hz, CH$_2$CH$_3$), 4.10 (2H, q, $J$ = 7.2 Hz, CH$_2$CH$_3$), 8.10 (2H, br s, NH$_2$). $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ (ppm) 14.03 (CH$_3$), 14.20 (CH$_3$), 50.0, 58.0, 60.1, 60.2, 113.0, 126.7, 127.8 (2C), 128.1 (2C), 140.0, 158.7, 162.9, 170.6, 172.6. IR (KBr, cm$^{-1}$): $\nu_{N-H}$ = 3303; $\nu_{C-O}$ = 3104; $\nu_{C=O}$ = 1731; $\nu_{C=O}$ = 1689. MS m/z (%): 434 (M$^+$, 20), 358 (M + H$^+$, Na; 36). Anal. Calcd for C$_{19}$H$_{24}$N$_2$O$_2$Se: C 49.76; H 5.16; N 10.24. Found: C 49.59; H 7.2; N 9.78.
36.6 (CH₂CO), 60.0 (OCH₂), 60.1 (OCH₂), 112.3 (C-5), 155.7 (C-4), 163.2, 169.2 (C-2 and C=O), 172.1 (C=O). IR (KBr, cm⁻¹): νₜₐₜ = 3351; νₙₗₗ = 3302; νₓᵧₓ = 1716; νₓᵧᵧ = 1691. MS m/z (%): 329 (M + H⁺, Na; 50). Anal. Calcd for C₁₀H₁₄N₂O₄Se: 39.36; H 4.62; N 9.18. Found: 39.11; H 4.68; N 9.55.

**Ethyl 2-(2-acetamino-5-ethoxycarbonyl-1,3-selenazol-4-yl)ethanoate (9). Method A.** To a solution of 2-acetamino-1,3-selenazole 4a (0.3 g, 0.86 mmol) in absolute ethanol (8 mL) triethylamine (0.15 g, 0.2 mL, 1.48 mmol) and ethanethiol (0.24 g, 0.28 mL, 3.9 mmol) were added. The reaction mixture was stirred under argon at rt for 5 days. The solvent was evaporated under reduced pressure, the resulting residue was diluted with dichloromethane (15 mL) and solid was removed by filtration. The extract was washed with 1M sulphuric acid (15 mL), brine (15 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the residue material was subjected to flash chromatography with silica gel using a solvent gradient (from 20 to 50% ethyl acetate in hexane) to give the title compound 9 as white crystals (0.142 g, 60%), mp 141-142 °C (ethyl acetate – hexane).

**References and Notes**


13. The CCDC deposition number of ethyl 2-(2-amino-5-ethoxycarbonyl-1,3-selenazol-4-yl)-2-bromoethanoate (3) is 729374; formula: C_{10}H_{13}BrN_{2}O_{4}Se; unit cell parameters: a 8.2371(3), b 18.5712(9), c 9.0273(3), β 94.695(3); space group: P 21/c.