An Efficient Access to Selenazoline-4-Carboxylate Derivatives Incorporating Cyclopropyl Groups

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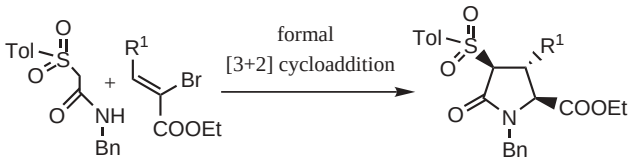
Abstract: 5-Spirocyclopropane-annulated selenazoline-4-carboxylates were synthesized in good yield via Michael addition of selenoamide to 2-bromo-2-cyclopropylideneacetate followed by an intramolecular substitution under basic conditions ($NaHCO_3$, MeCN).

Key words: Michael addition, selenoamide, selenium heterocycles



Scheme 1

A variety of simple cyclopropane-containing compounds have been of synthetic interest due to their biological activity.[1] These include cyclopropylamine, cyclopropylmethanols, cyclopropyl-substituted ketones, and especially the cyclopropane-derived amino acids, which have attractive attention as photochemical agents, enzyme, inhibitors, or probes in metabolism studies.[2]

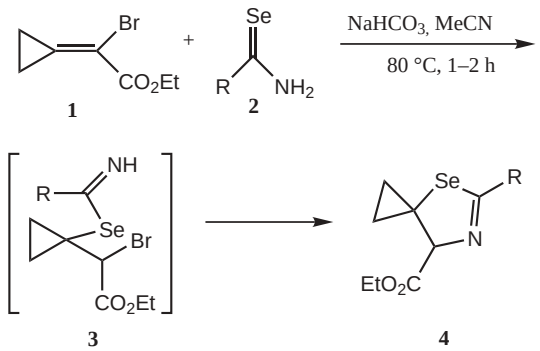
The selenium heterocycles are of marked interest because of their antitumor, antibacterical and other notable activities.[3] Among our efforts devoted to the chemistry of selenium,[4] we were interested in the synthesis of spirocyclopropane-annulated selenium heterocyclic compounds. At present, this kind of selenium compounds was not available in literatures. It is expected that this kind of heterocycles can be used as biologically active compounds.

Methylenecyclopropanes (MCPs), which are highly strained but readily accessible molecules, have served as useful building blocks in organic synthesis.[5] They can undergo a variety of reactions because the relief of ring strain provides a potent thermodynamic driving force for this process. Over the last decades, increasing attention has been paid to the synthesis transformation of MCPs, which have been employed for the construction of complex organic molecules.[6] Also many unnatural molecules containing cyclopropane, which exhibit some interesting characters, had been synthesized by MCPs through ring-untouched reactions.[7]

Recently, Chang has reported a base-induced coupling/cyclization reaction of α-sulfonylacetamide with ethyl (*Z*)-2-bromo-2-propenoates (Scheme 1).[8]

In the above reaction, α-sulfonylacetamide was used as an efficient dinucleophile. Selenoamide[9] is also a good dinucleophile, so we prepared to synthesize a new kind of selenium heterocycles containing cyclopropane by using selenoamide and 2-bromo-2-cyclopropylideneacetate.

At the first attempt, we examined the reaction of 2-bromo-2-cyclo-propylideneacetates **1** with phenylselenoamide **2a** in THF in the presence of Et_3N. After workup and isolation, the desired product, 5-spirocyclopropane-annulated selenazoline-4-carboxylates **4a** was obtained in 65% yield. The structure was assigned on the basis of its ^1H NMR, ^{13}C NMR, IR spectra, MS data and microanalyses. The possible mechanism may involve a Michael addition followed by an intramolecular nucleophilic substitution (Scheme 2). Further screening demonstrated anhydrous MeCN and $NaHCO_3$ were more suitable conditions for the mentioned reaction and the yield of **4a** could be improved up to 85%. Under the same condition, a series of selenoamides were chosen as substrates and 5-spirocyclopropane-annulated selenazoline-4-carboxylates were obtained in good yields (Table 1). However, owing to the instability and the difficulty of purification of alkylselenocarboxamide,[13] we succeeded in our experiment using **2i**, which was added directly to the reaction system without purification, and obtained **4i** in 70% yield.



Scheme 2

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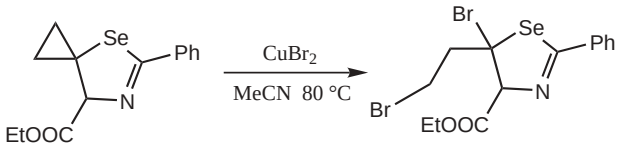
Table 1 One Pot Synthesis of selenazoline-4-carboxylates[10]

Entry	R	Product	Yield (%)[a]
1	Ph	**4a**	85
2	*p*-ClC_6H_4	**4b**	83
3	*p*-BrC_6H_4	**4c**	75
4	*m*-BrC_6H_4	**4d**	82
5	*p*-$CH_3C_6H_4$	**4e**	79
6	*m*-$CH_3C_6H_4$	**4f**	88
7	*p*-FC_6H_4	**4g**	84
8	3,4-$(OCH_2O)C_6H_3$	**4h**	81
9	$PhCH_2$[b]	**4i**	70

[a] Overall yields based on ethyl 2-bromo-2-cyclopropylideneacetate.
[b] Prepared from $PhCH_2CN$ (5 mmol) + NaSeH (10 mmol)

Recently, our group reported a CuX_2-mediated cyclization reaction of cyclopropylideneacetic acids or esters and a CuX_2-mediated halogenation of alkylidenecyclopropanes.[11] Considering the structure of **4a**, which has a cyclopropyl group, we presumed that the cyclopropyl ring could be opened and be halogenated under the same conditions.[11] As excepted, we obtained compound **5a** in 82% (Scheme 3).[12] It has two different kind of bromine atoms in one molecular unit, which could be further transformed. Further applications are being investigated in our laboratory.



4a **5a** 82%

Scheme 3

In summary, we have developed an efficient method for the preparation of 5-spirocyclopropane-annulated selenazoline-4-carboxylate derivatives. It is expected that this kind of selenazoline derives could be used as biologically active compounds.[3]

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(10) **Typical Procedure for the Synthesis of 4**: A solution of the respective ethyl-2-bromo-2-cyclopropylideneacetate[2] (**1**) (0.5 mmol), selenoamide[13] **2** (0.5mmol), and $NaHCO_3$ (1.00 g, 11.9 mmol) in freshly distilled MeCN (10 mL) was heated under reflux for 1–2 h. After filtration, the solvent was

evaporated in vacuo. The residue was subjected to preparative TLC (eluent: petroleum ether–Et_2O, 3:1) to afford the product **4**.

4a: IR (film): 3062, 2981, 1747, 1729, 1255, 1180 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.76–7.78 (m, 2 H), 7.46–7.48 (m, 1 H), 7.39–7.43 (m, 2 H), 4.83 (s, 1 H), 4.20–4.25 (q, *J* = 7.1 Hz, 2 H), 1.27–1.31 (t, *J* = 7.1 Hz, 3 H), 1.13–1.17 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 171.27, 168.44, 135.60, 131.60, 128.96, 128.60, 86.01, 61.34, 32.13, 16.63, 14.30, 9.36. MS (EI): *m*/*z*: 309 (4.64) [$M^+(Se^{80})$], 236 (100). Anal. Calcd for $C_{14}H_{15}NO_2Se$: C, 54.55, H, 4.91, N, 4.54. Found: C, 54.70; H, 4.98; N, 4.50.

4b: IR (film): 3067, 2981, 1747, 1730, 1181, 1092 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.69–7.72 (d, *J* = 8.8 Hz, 2 H), 7.38–7.40 (d, *J* = 8.8 Hz, 2 H), 4.82 (s, 1 H), 4.21–4.26 (q, *J* = 7.1 Hz, 2 H), 1.31–1.28 (t, *J* = 7.1 Hz, 3 H), 1.14–1.18 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 169.93, 168.27, 137.68, 134.08, 130.16, 128.83, 85.97, 61.41, 32.57, 16.57, 14.29, 9.36. MS (EI): *m*/*z* = 343 (5.43) [$M^+(Se^{80},Cl^{35})$], 270 (100). Anal. Calcd for $C_{14}H_{14}ClNO_2Se$: C, 49.07; H, 4.12; N, 4.09. Found: C, 48.81; H, 4.20; N, 4.20.

4c: IR (film): 3065, 2980, 1745, 1729, 1179, 1096 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.63–7.65 (d, *J* = 8.4 Hz, 2 H), 7.54–7.56 (d, *J* = 8.4 Hz, 2 H), 4.81 (s, 1 H), 4.20–4.26 (q, *J* = 7.1 Hz, 2 H), 1.28–1.31 (t, *J* = 7.1 Hz, 3 H), 1.14–1.17 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 170.05, 168.23, 134.54, 131.80, 130.33, 126.16, 86.02, 61.41, 32.57, 16.57, 14.27, 9.37. MS (EI): *m*/*z* = 387 (4.23) [$M^+(Se^{80},Br^{79})$], 97 (100), 314 (23.72). Anal. Calcd for $C_{14}H_{14}BrNO_2Se$: C, 43.43; H, 3.65; N, 3.62. Found: C, 43.55; H, 3.72; N, 3.60.

4d: IR (film): 3065, 2891, 1746,1730, 1245, 1281 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.96–7.97 (t, *J* = 1.7 Hz, 1 H), 7.59–7.66 (m, 2 H), 7.27–7.31 (t, *J* = 7.8 Hz, 1 H), 4.83 (s, 1 H), 4.19–4.25 (q, *J* = 7.1 Hz, 2 H), 1.28–1.32 (t, *J* = 7.1 Hz, 3 H) 1.14–1.18 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 169.73, 168.17, 137.45, 134.44, 131.39, 130.07, 127.81, 122.75, 85.96, 61.45, 32.57, 16.55, 14.28, 9.39. MS (EI): *m*/*z* = 387 (4.23) [$M^+(Se^{80},Br^{79})$], 314 (100). Anal. Calcd for $C_{14}H_{14}BrNO_2Se$: C, 43.43; H, 3.65; N, 3.62. Found: C, 43.23; H, 3.73; N, 3.60.

4e: IR (film): 3063, 2980, 1747, 1728, 1255, 1179 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.65–7.67 (d, *J* = 8.1 Hz, 2 H), 7.20–7.22 (d, *J* = 8.1 Hz, 2 H), 4.81 (s, 1 H), 4.17–4.23 (q, *J* = 7.1 Hz, 2 H), 2.39 (s, 3 H), 1.27–1.31 (t, *J* = 7.1 Hz, 3 H), 1.13–1.17 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 171.05, 168.57, 142.07, 133.03, 129.26, 128.94, 86.00, 61.28, 32.00, 21.52, 16.62, 14.28, 9.34. MS (EI): *m*/*z* = 323 (3.28) [$M^+(Se^{80})$], 250(100). Anal. Calcd for $C_{15}H_{17}NO_2Se$: C, 55.91; H, 5.32; N, 4.35. Found: C, 55.79; H, 5.40; N, 4.41.

4f: IR (film): 3065, 2981, 1746,1729, 1265, 1181 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.64 (s, 1 H), 7.55–7.56 (m, 1 H), 7.29–7.30 (m, 2 H), 4.83 (s, 1 H), 4.22–4.25 (q, *J* = 7.1 Hz, 2 H), 2.39 (s, 3 H), 1.28–1.31 (t, *J* = 7.1 Hz, 3 H), 1.14–1.17 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 171.40, 168.25, 138.49, 135.14, 132.71, 129.32, 128.56, 126.54, 85.38, 61.43, 31.89, 21.22, 16.81, 14.29, 9.23. MS (EI): *m*/*z* = 323 (3.83) [$M^+(Se^{80})$], 250 (100).; Anal. Calcd for $C_{15}H_{17}NO_2Se$: C, 55.91; H, 5.32; N, 4.35. Found: C, 56.08; H, 5.21; N, 4.42.

4g: IR (film): 3063, 2982, 1732, 1253, 1182 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.75–7.79 (m, 2 H), 7.08–7.12 (m, 2 H), 4.81 (s, 1 H), 4.20–4.24 (q, *J* = 7.1 Hz, 2 H), 1.28–1.32 (t, *J* = 7.1 Hz, 3 H), 1.14–1.18 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 171.27, 168.36, 164.73 (d, *J* = 250.9 Hz), 131.96 (d, *J* = 3.1 Hz), 131.03 (d, *J* = 8.7 Hz), 115.66 (d, *J* = 22 Hz), 85.96, 61.37, 32.58, 16.57, 14.27, 9.32; MS (EI): *m*/*z* = 327 (2.60) [$M^+(Se^{80})$], 254 (100). Anal. Calcd for $C_{14}H_{14}FNO_2Se$: C, 51.54; H, 4.33; N, 4.29. Found: C, 51.69; H, 4.40; N, 4.13.

4h: IR (film): 3064, 2981, 1747, 1727, 1254, 1037 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.35 (s, 1 H), 7.21–7.24 (m, 1 H), 6.80–6.82 (d, *J* = 8.0 Hz, 1 H), 6.02 (s, 2 H), 4.78 (s, 1 H), 4.18–4.25 (q, *J* = 7.1 Hz, 2 H), 1.27–1.31 (t, *J* = 7.1 Hz, 3 H), 1.13–1.16 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 170.02, 168.56, 150.50, 147.98, 130.08, 125.00, 108.17, 108.04, 101.73, 85.81, 61.30, 32.22, 16.60, 14.29, 9.27. MS (EI): *m*/*z* = 353 (1.03) [$M^+(Se^{80})$], 84 (100), 280 (17.15). Anal. Calcd for $C_{15}H_{15}NO_4Se$: C, 51.15; H, 4.29; N, 3.98 Found: C, 51.00; H, 4.38; N, 4.08.

4i: IR (film): 3065, 2980, 1746, 1728, 1252, 1105 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.29–7.40 (m, 5 H), 4.81 (s, 1 H), 4.30 (s, 2 H), 4.20–4.25 (q, *J* = 7.1 Hz, 2 H), 1.27–1.31 (t, *J* = 7.1 Hz, 3 H), 1.14–1.18 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 171.11, 168.40, 135.35, 129.10, 128.45, 127.78, 85.98, 61.29, 43.10, 32.04, 16.53, 14.29, 9.35. MS (EI): *m*/*z* = 323 (3.60) [$M^+(Se^{80})$]. Anal. Calcd for $C_{15}H_{17}NO_2Se$: C, 55.91; H, 5.32; N, 4.35; Found: C, 55.80; H, 5.40; N, 4.20.

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(12) Typical procedure: A solution of **4a** (171 mg, 0.5 mmol) with $CuBr_2$ (450 mg, 2 mmol) in MeCN (10 mL) was stirred under reflux and was monitored by TLC. After the reaction was completed, the mixture was diluted with 20 mL of sat. NH_4Cl and then extracted with Et_2O (3 ×). The Et_2O phases were combined and dried over $MgSO_4$. After evaporation, the residue was subjected to preparative TLC (eluent: petroleum ether–Et_2O, 3:1) to afford **5a** 192mg (82%). IR(film): 3061, 2980, 1735 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.99–8.01 (m, 2 H), 7.52–7.56 (m, 1 H), 7.42–7.48 (m, 2 H), 5.00 (s, 1 H), 4.25–4.34 (m, 2 H), 3.70–3.90 (m, 4 H), 1.33–1.37 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 169.22, 165.13, 132.78, 129.19, 128.88, 126.62, 86.62, 74.59, 62.55, 36.50, 32.39, 14.47. MS (EI): *m*/*z* = 467 (0.58) [$M^+(Se^{80},Br^{79},Br^{79})$]. Anal. Calcd for $C_{14}H_{15}Br_2NO_2Se$: C, 35.93; H, 3.23; N, 2.99. Found: C, 36.90; H, 3.41; N, 3.10.

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