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# Selective synthesis of novel 2-imino-1,3-selenazolidin-4-ones and 2-amino-1,3,4-selenadiazin-5-ones from isoselenocyanates

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ABSTRACT

An efficient and regioselective synthesis of 2-imino-1,3-selenazolidin-4-ones and 2-amino-1,3,4-selenadiazin-5-ones was achieved via one-pot reaction of isoselenocyanates, hydrazines, and ethyl chloroacetate or chloroacetyl chloride, respectively. Plausible mechanisms for these transformations were given.



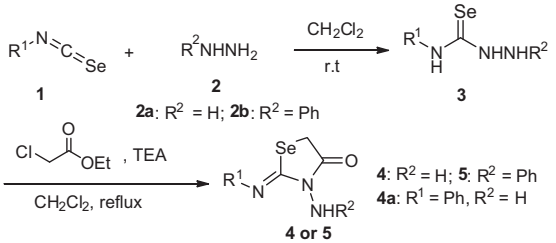
Recently, the synthesis of selenium-containing heterocycles has attracted much attention due to their biological and pharmaceutical activities.[1] It has been widely reported that selenium-containing heterocycles can be used as antioxidant,[2] antiinflammatory,[3] antibacterial,[4] antiviral,[5] and antitumor[6] agents. Therefore, many organoselenium reagents have been developed to introduce selenium into heterocycles.[7] Isoselenocyanates have emerged as one of the most efficient organoselenium reagents for their convenient preparation, low toxicity, relative stability, and excellent reactivity.[8] For example, isoselenocyanates have been widely utilized in the preparation of various selenium-containing heterocycles, such as 1,3-selenazolidines, 1,3-selenazines, 1,3-selenazine-4-ones, selenazetidines, selenophenes, 1,3-oxaselenolanes, selenazepines, and 1,3-oxaselenepanes.[9]

To the best of our knowledge, however, only a few papers describe the preparation of 1,3-selenazolidine derivatives, and only one procedure reports the preparation of 1,3-selenazolidin-4-ones from *N,N'*-disubstituted selenoureas.[10] Herein we wish to report the synthesis of novel 1,3-selenazolidin-4-ones from isoselenocyanates.

Primarily, we investigated the one-pot reaction of isoselenocyanates, hydrazines and ethyl chloroacetate (Scheme 1). Selenosemicarbazide[11] **3a** was obtained easily by mixing isoselenocyanatobenzene with hydrazine hydrate at room temperature in $CH_2Cl_2$. Without separation of **3a**, ethyl chloroacetate was added and the resulting mixture was stirred at room temperature for 12 h. However, no desired product **4a** was detected.

Accordingly, the reaction mixture was refluxed in $CH_2Cl_2$ with stirring for 12 h, and about 25% selenosemicarbazide **3a** was converted to product **4a**. Considering that the HCl released during the reaction might affect the conversion, acid trapper was added to the reaction mixture.[12] Various bases, such as NaOH, $NaHCO_3$, $Na_2CO_3$, KOH, and triethylamine (TEA) were investigated, and TEA was found to be the optimal one. To further improve the yield, a number of solvents including THF, DMF, MeCN, EtOH, $CH_2Cl_2$, and $CHCl_3$ were screened. Unfortunately, deselenization was observed when THF, DMF, MeCN, or EtOH was used as the solvent. $CHCl_3$ seemed to be the promising solvent for the reaction since 83% yield could be obtained (Table 1, entry 10). Further investigation found that the reaction performed in $CH_2Cl_2$ required lower temperature and shorter time and afforded comparable yields (Table 1, entry 5). Thus, $CH_2Cl_2$ was established as the optimal solvent.

Under the standard conditions, the addition of isoselenocyanates **1**, hydrazine hydrates **2a**, and ethyl chloroacetate was performed in the presence of triethylamine. And 3-amino-2-aryli-




**Scheme 1.** Preparation of 2-imino-1,3-selenazolidine-4-ones **4** or **5** from isoselenocyanates.

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**Table 1**
Optimization of reaction conditions

| Entry | Solvent | Base | Temp (°C) | Time[a] (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | NaOH | reflux | 20 | <10 |
| 2 | $CH_2Cl_2$ | $NaHCO_3$ | relfux | 20 | <10 |
| 3 | $CH_2Cl_2$ | $Na_2CO_3$ | reflux | 20 | <10 |
| 4 | $CH_2Cl_2$ | KOH | reflux | 20 | <10 |
| 5 | $CH_2Cl_2$ | TEA | reflux | 15 | 85 |
| 6 | THF | TEA | 25 | 5 | Trace |
| 7 | DMF | TEA | 25 | 4 | Trace |
| 8 | MeCN | TEA | 25 | 8 | Trace |
| 9 | EtOH | TEA | reflux | 7 | Trace |
| 10 | $CHCl_3$ | TEA | reflux | 24 | 83 |

[a] Monitored by TLC.
[b] Isolated yields based on **1**.

**Table 2**
Preparation of 2-imino-1,3-selenazodin-4-ones **4** and **5**[a]

| Entry | $R^1$ | $R^2$ | Compounds **3** | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | Ph | H | **3a** | **4a** | 85 |
| 2 | 4-MeOPh | H | **3b** | **4b** | 90 |
| 3 | 4-ClPh | H | **3c** | **4c** | 89 |
| 4 | 2-MePh | H | **3d** | **4d** | 86 |
| 5 | 2-EtPh | H | **3e** | **4e** | 88 |
| 6 | 3-MePh | H | **3f** | **4f** | 89 |
| 7 | 4-BrPh | H | **3g** | **4g** | 85 |
| 8 | 1-Naphthyl | H | **3h** | **4h** | 82 |
| 9 | Cyclohexyl | H | **3i** | **4i** | 78 |
| 10 | 4-MeOPh | Ph | **3j** | **5a** | 65 |
| 11 | 4-ClPh | Ph | **3k** | **5b** | 57 |
| 12 | 1-Naphthyl | Ph | **3l** | **5c** | 61 |
| 13 | 2-MePh | Ph | **3m** | **5d** | 63 |
| 14 | 2-EtPh | Ph | **3n** | **5e** | 60 |
| 15 | Ph | Ph | **3o** | **5f** | None |

[a] One-pot reaction of isoselenocyanate (1 mmol), hydrazine (1 mmol) and ethyl chloroacetate (1.5 mmol).
[b] Isolated yields based on **1**.

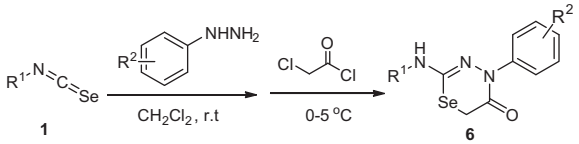
mino-1,3-selenazolidin-4-one derivatives **4** were obtained in good to excellent yields (Table 2, entries 1–9).[12] The $R^1$ group on the isoselenocyanates had little effect on both reaction rates and yields. Aryl-substituted isoselenocyanates (Table 2, entries 1–8) gave slightly higher yields than alkyl-substituted isoselenocyanate (Table 2, entry 9).

The reaction showed high regioselectivity to afford five-membered ring products. In all reactions 3-amino-2-arylimino-1,3-selenazolidine-4-ones **4** were obtained as the major products and their structures were confirmed by spectroscopic analysis. $^1$H NMR spectra showed the presence of two amino protons ($-NH_2$). To further demonstrate the structure, compound **4b** was treated with benzaldehyde in ethanol under reflux and compound **7** was obtained (Scheme 2). Thus, it was unambiguously ascertained that the products were five-membered ring compound **4**, rather than six-membered ring compound **6**.

Afterward, phenylhydrazine **2b** was employed to react with isoselenocyanates **1** and ethyl chloroacetate in one-pot, correspondingly, 3-phenylamino-2-arylimino-1,3-selenazolidin-4-ones **5** were obtained. Compared with **2a**, the reaction with phenylhydrazine **2b** was less efficient and **5** was obtained in relatively lower yields. Although the steric hindrance and electron-withdrawing effect of phenyl on the hydrazine influenced the efficiency of the cyclization, $R^1$ showed only very slight influence (Table 2, entries 10–14).

Amazingly, when $R^1$ was phenyl group (Table 2, entry 15), no target product was obtained. For this reason, additional experiments using chloroacetyl chloride, instead of ethyl chloroacetate were performed (Scheme 3). We expected that the more reactive reagent chloroacetyl chloride could react with **3** to afford the desired products **5**. However, it was observed that the polarity of this new product (**6a**) was stronger than that of compounds **5a** according to TLC analysis. Furthermore, $^1$H NMR spectra showed that the protons of $CH_2Se$ group on **5a** were located at above 4.0 ppm, while those of **6a** were observed below 4.0 ppm. $^{13}$C NMR spectra showed the signal of the carbonyl at ca. 170 and 160 ppm for compounds **5a** and **6a**, respectively. We deduced that compounds **6a** were six-membered ring products, named as 2-amino-1,3,4-selenadiazin-5-one. The structures of **5a** and **6a** were further confirmed by HSQC and HMBC. The carbonyl of **5a** was correlative to proton on NH, while the carbonyl of **6a** was not (Fig. 1).

Before the preparation of more six-membered ring products **6**, the reaction conditions were further optimized. The cyclization of




**Scheme 3.** Preparation of 2-arylamino-1,3,4-selenadiazin-5-ones **6** from isoselenocyanates.

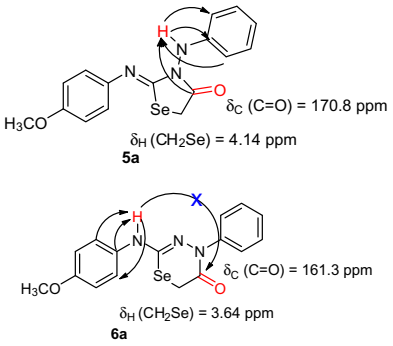
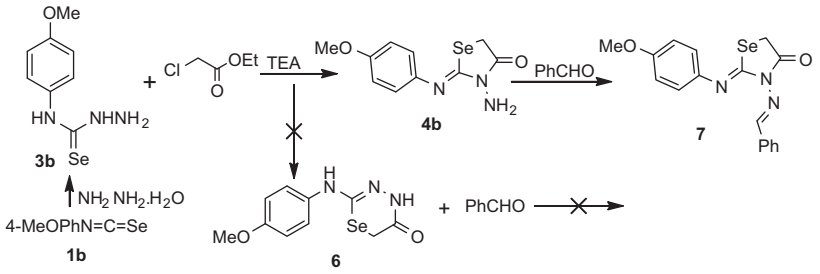
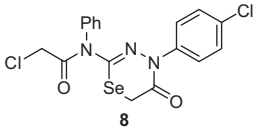



**Figure 1.** HMBC correlations involving NH of **5a** and **6a**.




**Scheme 2.** Further demonstration of the structure of **4**.

intermediates selenosemicarbazides **3** with chloroacetic chloride was conducted in $CH_2Cl_2$ without using acid trapper (Scheme 3). The reaction was significantly affected by temperature, especially when there was substituent on the phenylhydrazine. Good to excellent yields of **6** were obtained when the reaction was performed at 0–5 °C. A suitable ratio of chloroacetyl chloride to isoselenocyanates **1** was also important. Excess chloroacetyl chloride would lead to the formation of side product **8**. The optimized ratio of chloroacetyl chloride to isoselenocyanates **1** was 1.2:1.




**8**

On the basis of the above results, a variety of 2-amino-1,3,4-selenadiazin-5-ones **6** were obtained from isoselenocyanates in good to excellent yields. The results were summarized in Table 3.[13] Introduction of electron donating group to phenylhydrazine increased reaction yields (Table 3, entries 6–8). The reaction also showed high regioselectivity for the formation of **6**. Five-membered ring products **5** were undetected under the reaction conditions.

It has been reported that the reaction of selenosemicarbazide with ω-bromoacetophenone would give six-membered ring products 1,3,4-selenadiazine.[14] While we herein have reported a method for selective synthesis of both five-membered ring compounds 1,3-selenazolidin-4-ones and six-membered ring compounds 1,3,4-selenadiazin-5-ones.

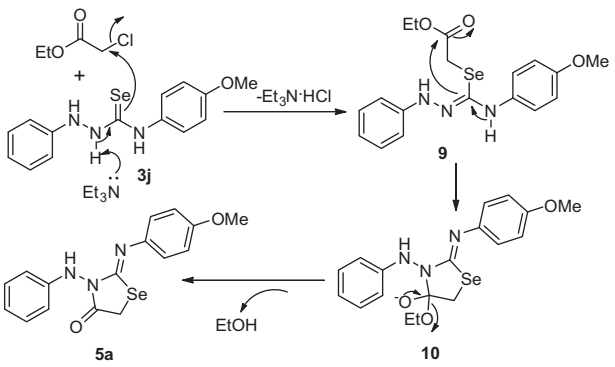
Based on the literature[14] and the results of our study, plausible mechanisms were proposed for the formation of **5a** and **6a**, respectively. As shown in Scheme 4, selenosemicarbazide **3j** obtained from isoselenocyanate **1b** was reacted with ethyl chloroacetate to form intermediate **9**, which then cyclized to **10**. Successively, **10** was converted to the final product **5a** by intramolecular elimination. Compared with ethyl chloroacetate, chloroacetyl chloride was much more reactive. Thus selenosemicarbazide **3j** reacted with chloroacetyl chloride easily to afford intermediate **11** without an acid trapper, and then **11** cyclized to the ultimate product **6a** rapidly (Scheme 5). The above proposed mechanism shed light on the high regioselectivity associated with the reaction.

In summary, the one-pot condensation of isoselenocyanate, hydrazine, and ethyl chloroacetate afforded 2-imino-1,3-selenazolidin-4-ones in good to excellent yields; while the reaction of isoselenocyanate, hydrazine and chloroacetyl chloride provided a practical and high efficient approach to 2-amino-1,3,4-selenadiazin-5-ones. The one-pot procedure showed high regioselectivity and may find broader applications in the synthesis of selenium-containing five- and six-membered heterocycles.

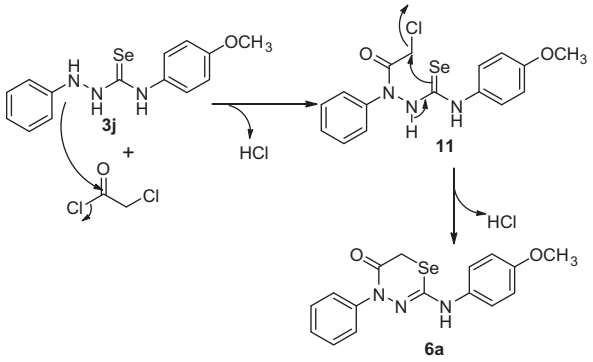
**Table 3**
Preparation of 2-arylamino-1,3,4-selenadiazin-5-ones **6**[a]

| Entry | $R^1$ | $R^2$ | Compounds **3** | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 4-MeOPh | H | **3j** | **6a** | 92 |
| 2 | 4-ClPh | H | **3k** | **6b** | 81 |
| 3 | 1-Naphthyl | H | **3l** | **6c** | 80 |
| 4 | 2-MePh | H | **3m** | **6d** | 85 |
| 5 | Ph | H | **3o** | **6e** | 86 |
| 6 | 1-Naphthyl | 2-Et | **3p** | **6f** | 90 |
| 7 | 4-ClPh | 2-Et | **3q** | **6g** | 88 |
| 8 | 4-MeOPh | 2-Et | **3r** | **6h** | 92 |
| 9 | Ph | 4-Cl | **3s** | **6i** | 80 |
| 10 | 2-MePh | 4-Cl | **3t** | **6j** | 79 |
| 11 | 4-MeOPh | 4-Cl | **3u** | **6k** | 82 |
| 12 | 4-ClPh | 4-Cl | **3v** | **6l** | 75 |

[a] One-pot reaction of isoselenocyanate (1 mmol), hydrazine (1 mmol) and chloroacetic chloride (1.2 mmol).
[b] Isolated yields based on **1**.




**Scheme 4.** A plausible mechanism proposed for the formation of **5a**.




**Scheme 5.** A plausible mechanism proposed for the formation of **6a**.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.068.

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12. Typical procedure for the preparation of 2-imino-1,3-selenazolidin-4-ones **4** and **5** (**4a** was selected as example): A mixture of isoselenocyanates **1a** (0.182 g, 1 mmol) and 85% hydrazine hydrate (0.059 g, 1 mmol) in $CH_2Cl_2$ (10 ml) was stirred at room temperature until total consumption of the starting material (TLC, 1 h). Then ethyl chloroacetate (0.184 g, 1.5 mmol) and triethylamine (0.101 g, 1 mmol) were added and the resulting mixture was stirred at reflux temperature. After the completion of the reaction, the reaction mixture was evaporated under vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to give **4a** (0.217 g, 85%) as white solid. Mp: 101.5–102.1 °C; IR (KBr): $\nu_{max}$ = 3317, 3240, 1697, 1633, 1590 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 7.38 (t, $J$ = 7.6 Hz, 2H, ArH), 7.16 (t, $J$ = 7.6 Hz, 1H, ArH), 6.94 (d, $J$ = 7.6 Hz, 2H, ArH), 5.39 (br, 2H, $NH_2$), 3.98 (s, 2H, $CH_2$); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 169.6, 150.3, 149.2, 129.5 (CH × 2), 124.5, 120.5 (CH × 2), 23.5; MS (EI): $m/z$ (%) = 251 (22), 253 (49), 255 ($M^+$, 100); HRMS-ESI: calcd for $C_9H_{10}N_3OSe$ $(M+H)^+$: 255.9989; found: 255.9983.
13. Typical procedure for the preparation of 2-amino-1,3,4-selenadiazin-5-ones **6** (**6a** was selected as example): A mixture of isoselenocyanates **1b** (0.212 g, 1 mmol) and phenylhydrazine (0.108 g, 1 mmol) in $CH_2Cl_2$ (10 ml) was stirred at room temperature until total consumption of the starting material (TLC, 1 h). Then chloroacetic chloride (0.136 g, 1.2 mmol) was added dropwise at 0–5 °C, and the resulting mixture was stirred at this temperature for 0.5 h. After the completion of the reaction, the reaction mixture was evaporated under vacuum. The residue was purified by flash on silica gel (petroleum ether/ethyl acetate, 4:1) to give **6a** (0.285 g, 86%) as faint yellow solid. Mp: 186.4–187.1 °C; IR (KBr): $\nu_{max}$ = 3269, 1627, 1590, 1573, 1490 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ = 9.37 (s, 1H, NH), 7.56 (d, $J$ = 8.4 Hz, 2H, ArH), 7.49 (d, $J$ = 8. 0 Hz, 2H, ArH), 7.42 (t, $J$ = 8.0 Hz, 2H, ArH), 7.28–7.21 (m, 3H, ArH), 6.95 (t, $J$ = 7.6 Hz, 1H, ArH), 3.68 (s, 2H, $CH_2$); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ = 161.2, 144.4, 141.9, 140.7, 128.7 (CH × 2), 128.4 (CH × 2), 126.1, 124.8 (CH × 2), 122.2, 118.6 (CH × 2), 22.0; MS (ESI): $m/z$ (%) = 330 (49), 332 ($M^+$+1, 100); HRMS-ESI: calcd for $C_{15}H_{14}N_3OSe$ $(M+H)^+$: 332.0302; found: 332.0301.
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