Reaction of Primary Selenoamides with Bisacyl Chlorides: Syntheses of 6-Hydroxy-1,3-selenazin-4-ones and Selenoanhydrides

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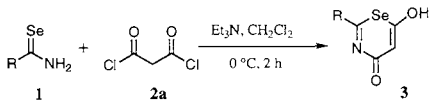
The reaction of primary selenoamides with bisacyl chlorides in the presence of Et_3N was investigated. By the reaction with malonyl chloride, 6-hydroxy-1,3-selenazin-4-ones were provided in high yield. By the reactions with succinyl chloride, glutaryl chloride, and phthaloyl chloride, the corresponding selenoanhydrides were obtained in moderate yields, respectively.

Much attention has been given to the chemistry of organoselenium compounds, because they show high reaction activities as synthetic tools and often have unique biological and medicinal effects.[1] Since selenoamides have an active carbon-selenium double bond as well as an intrinsic Se-C-N unit, their reactivities are particularly interesting. However, few reports have been published on the reactivities of selenoamides[2] compared with those of thioamides,[3] because the essential selenium-containing starting materials are less readily available than the analogous sulfur intermediates, and the primary selenoamides are difficult to prepare. We previously investigated a convenient method for the synthesis of potassium selenocarboxylates.[4] The primary selenoamides were synthesized using the potassium selenocarboxylates to introduce selenium under mild conditions.[5] Here, we wish to describe the reactions of primary selenoamides with bisacyl chlorides.



1 2a 3

Scheme 1.

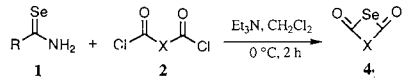
The typical procedure for the synthesis of 6-hydroxy-2-*p*-tolyl-1,3-selenazin-4-one **3a** is described. To a 10 mL CH_2Cl_2 solution of *p*-tolylselenoamide **1a**, malonyl chloride (1 equiv.) **2a**, and Et_3N (2 equiv.) were added and the solution was stirred at 0 °C for 2 h under an argon atmosphere. After usual workup, **3a** was obtained in 62.5% yield (0.167 g) as an orange crystal.[6] In a similar manner, 6-hydroxy-1,3-selenazin-4-ones were obtained in moderate to high yields with malonyl chloride from a variety of primary selenoamides (Table 1). Hexaneselenoamide gave likewise the corresponding 1,3-selenazin-4-one in 60.6% yield In the IR spectra of **3**, the strong absorption of the OH group was seen at 3442 ± 13 cm^{-1}. The peak of the OH group and that of C5 (not CH_2, but CH) were also confirmed by ^1H and DEPT NMR spectra. From these results of the IR and NMR spectra, it was clarified that **3** is not 5*H*-1,3-selenazine-4,6-dione but the more stable 6-hydroxy-1,3-selenazin-4-one bearing an intramolecular ring conjugated system.

The reactions of **1a** with succinyl chloride **2b**, glutaryl chloride **2c**, and phthaloyl chloride **2d** were carried out in the same manner as above and gave the corresponding selenoanhydrides **4** in moderate yields. The yields of **4** are shown in Table 1. The acylation of selenoamide with bisacyl chloride is presumed to proceed via *Se*-acylation in the initial step. Subsequently, the selenium presumably attacks the other carbonyl carbon and ultimately leads to selenoanhydride **4**, because the reactions gave the corresponding *p*-tolunitrile generated from **1a** as a by-product.

Table 1. Reaction of primary seleno- or thioamide with bisacyl chloride

Primary amide[a]	Bisacyl chloride	Product	Yield (%)[b] with Et_3N	Yield (%)[b] without Et_3N
1a	2a	3a	62.5	43.2
1b	2a	3b	62.8	42.8
1c	2a	3c	71.6	28.6
1d	2a	3d	55.0	36.6
1a	2b	4a	36.3	21.6
1a	2c	4b	54.2	15.9
1a	2d	4c	59.6	41.0
5a	2a	6	43.0	93.1
5a	2d	7	23.6	71.6

a: R_1=4-$CH_3C_6H_4$, R_2=C_6H_5, R_3=4-$CH_3OC_6H_4$, R_4=2-ClC_6H_4; b: Isolated yield.;



1 2 4

Scheme 2.

The reaction of thiobenzamide with **2a** gave the corresponding 1,3-thiazine derivative **6**[7] in a similar route to 1,3-seleazine derivative given in the present reaction using selenoamide and **2a**. On the other hand, in the reactions with **2b**, **2c**, and **2d**, though thiobenzamide gave the corresponding *N*-thioacylimides **7**, respectively,[7] selenoamide gave the corresponding selenoanhydrides **4**. It has been reported that selenoamide, compared with the oxo- and thio-analogs, decreases overlapping of the carbon and selenium orbitals, which makes selenium more nucleophilic than sulfur.[8] That selenoanhydrides are formed much more readily than thioanhydrides upon treatment of the corresponding amides with a bisacyl chloride is presumably a consequence of the greater nucleophilicity of the selenocarbonyl selenium atom, as compared to the thiocarbonyl sulfur atom. Furthermore, in order to confirm the difference between the character of primary thioamide and that of selenoamide, several reactions were carried out with or without Et_3N (Table 1). In the case of selenoamide, the yields were increased in the presence of Et_3N, while in the case of thioamide the yields were higher in the absence of Et_3N. The reaction of **1a** with **2a** in the absence of Et_3N recovered **1a** in 24% yield. From these results, the following mechanism was speculated, though the elucidation of the reaction mechanism needs further studies. For the primary selenoamide the first step is acylation of selenium atom of the primary selenoamide, whereas for thioamide nitrogen atom of thioamide is acylated first. The difference in the site of first reaction might also explain the observations with and without Et_3N. In the case of selenoamide, the intermediate is a seleno-imidate [R-C(=NH)-Se-Ac] which is basic, but for thioamide that is a thio-imide [R-C(=S)-N-Ac] which is neutral, therefore, the presence or absence of Et_3N in the reaction system is reflected in the difference of yield.

Though there are many examples of the syntheses of thioanhydrides,[9] only a few articles regarding succinic and phthalic selenoanhydrides have been made available[10] and this is the first report of the synthesis of glutaric selenoanhydride.[11]

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6 Spectral data of 6-hydroxy-2-*p*-tolyl-1,3-selenazin-4-one (**3a**). Orange crystal.: mp 259.4-261.1°C; IR (KBr): 3448, 1685 cm^{-1}; ^1H NMR (DMSO) : δ 2.38 (s, 3H), 4.84 (s, 1H), 7.22 (d, *J*=8.4 Hz, 2H), 7.86 (d, *J*=8.8 Hz, 3H); ^{13}C NMR (DMSO) δ 21.2, 86.6 (CH), 127.3, 129.6, 137.7, 141.9, 171.6, 174.8, 176.5; ^{77}Se NMR (DMSO) δ 550.4; MS (CI) : *m/z* = 268 [M+1]; Found: C, 49.56; H, 3.51; N, 5.32%. Anal. Calcd for $C_{11}H_9NO_2Se$: C, 49.64; H, 3.41; N, 5.26%.

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11 Spectral data of glutaric selenoanhydride (**4b**). Orange oil; IR (neat): 1698 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 2.13-2.19 (m, 2H), 2.77 (t, *J*=12.0 Hz, 4H); ^{13}C NMR ($CDCl_3$) : δ 19.2, 43.6, 200.7; ^{77}Se NMR ($CDCl_3$) : δ 827.4; MS (CI) : *m/z* = 179 [M+1]; Found: C, 33.98; H, 3.49%. Anal. Calcd for $C_5H_6O_2Se$: C, 33.92; H, 3.42%.