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Generation and Reactions of a Selenoamide Dianion

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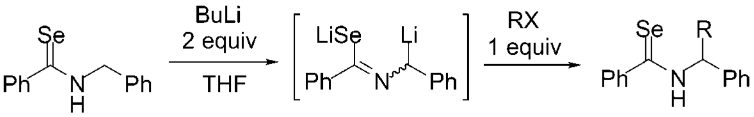
ABSTRACT



The selective generation of selenoamide monoanion and dianion was achieved by reacting *N*-benzyl selenobenzamide with BuLi. Alkylation of the dianion with 1 equiv of electrophile took place at the carbon atom adjacent to the nitrogen atom, and subsequent hydrolysis produced functionalized selenoamides in good to high yields. Ring opening of oxiranes using the dianion proceeded with high regio- and stereoselectivity to form *N*-3-hydroxy-1-phenylalkyl selenobenzamides. The stereochemistry of the major isomer derived from cyclohexene oxide was determined by X-ray molecular structure analysis.

The generation and reactions of dipole-stabilized carbanions adjacent to a nitrogen atom from secondary amides and secondary carbamates have been studied in great depth.[1] In contrast, much less attention has been paid to similar carbanions derived from substrates bearing selenocarbonyl groups. During our studies on selenium-atom-containing conjugate ions,[2] we have disclosed their electronic properties and reactions. Recently, we have also made progress in the synthesis and reactions of selenium isologues of amides, i.e., selenoamides.[3] For example, alkylation of tertiary selenoamides with alkyllithium was found to proceed smoothly to give unsymmetrically substituted ketones.[3e] We report here the selective generation and reactions of a selenoamide dianion from a secondary selenoamide with butyllithium (BuLi).

The *N*-benzyl selenoamide **1a**[4] was treated with 1 equiv of BuLi in THF at 0 °C for 30 min (Scheme 1). To the reaction mixture was added 2 equiv of ethyl iodide to give *Se*-ethyl selenoimide **4a** in high yield. More interestingly, in the reaction of selenoamide **1a** with 2 equiv of BuLi, the reaction mixture changed from orange to deep purple. The addition of 2 equiv of ethyl iodide quantitatively gave *Se*-ethyl selenoimide **5a**. These results imply that the monoanion **2a** was selectively formed from **1a** with 1 equiv of BuLi, and additional BuLi abstracted the proton at the carbon atom adjacent to the nitrogen atom of **1a** to form the dianion **3a**.[5,7] A similar reaction was observed for *N*-benzyl thioamide **1b**,[9]

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(1) (a) Tishler, N. A.; Tishler, H. M. *Tetrahedron Lett.* **1978**, 3−4. (b) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715−721. (c) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281−283. (d) Voyer, N.; Roby, J.; Chénard, S.; Barberis, C. *Tetrahedron Lett.* **1997**, *38*, 6505−6508.

(2) (a) Murai, T.; Hayakawa, S.; Kato, S. *Chem. Lett.* **2000**, 368−369. (b) Murai, T.; Kamoto, T.; Kato, S. *J. Am. Chem. Soc.* **2000**, *122*, 9850−9851. (c) Murai, T.; Hayakawa, S.; Kato, S. *J. Org. Chem.* **2001**, 66, 8101−8105.

(3) (a) Murai, T.; Ezaka, T.; Niwa, N.; Kanda, T.; Kato, S. *Synlett* **1996**, 865−866. (b) Murai, T.; Ezaka, T.; Kanda, T.; Kato, S. *J. Chem. Soc., Chem. Commun.* **1996**, 1809−1810. (c) Murai, T. Ezaka, T.; Ichimiya, T.; Kato, S. *Synlett* **1997**, 775−776. (d) Murai, T.; Mori, T.; Kato, S. *Synlett* **1998**, 619−620. (e) Murai, T.; Ezaka, T.; Kato, S. *Tetrahedron Lett.* **1998**, *39*, 4329−4332. (f) Murai, T.; Ezaka, T.; Kato, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1193−1200. (g) Murai, T.; Suzuki, A.; Ezaka, T.; Kato, S. *Org. Lett.* **2000**, *2*, 311−313. (h) Murai, T.; Mutoh, Y.; Kato, S. *Org. Lett.* **2001**, *3*, 1993−1995. (i) Murai, T.; Suzuki, A.; Kato, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2711−2716.

(4) Cohen, V. I. *J. Org. Chem.* **1977**, *42*, 2645−2647.

(5) In the reaction of *N*-benzyl amides with BuLi, ortho-metalation competed with a deprotonation from the benzylic carbon atom,[7] whereas the use of LDA in diglyme gave the dianion analogous to **3**.[1a]

(6) Simig, G.; Schlosser, M. *Tetrahedron Lett.* **1988**, *29*, 4277−4280.

(7) Our attempt to generate a similar carbanion α to a nitrogen atom from *N*,*N*-dibenzyl selenobenzamide with BuLi failed. Instead, butylation of the selenoamide took place to give valerophenone as a major product, as reported previously.[3e,8]

(8) Sekiguchi, M.; Ogawa, A.; Fujiwara, S.; Ryu, I.; Kambe, N.; Sonoda, N. *Chem. Lett.* **1990**, 2053−2056.

(9) The generation of a thioamide dianion similar to **3b** is rare but not unknown: Katritzky, A. R.; Denisko, O.; Lang, H. *Tetrahedron* **1995**, *51*, 8703−8710.

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Scheme 1

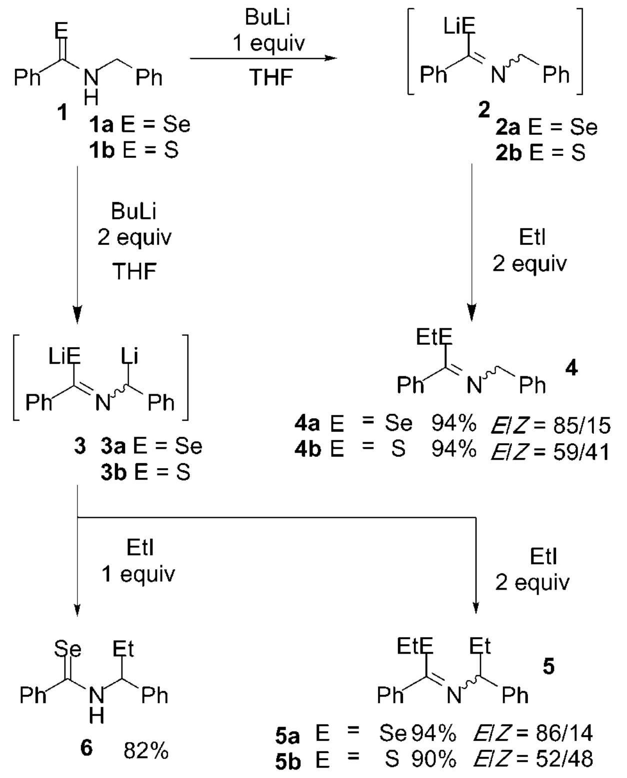
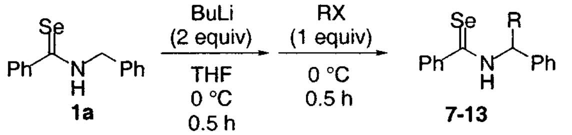
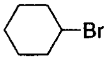
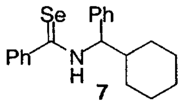
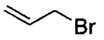
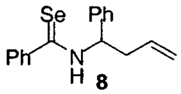
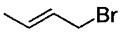
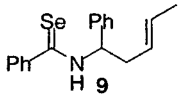
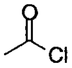
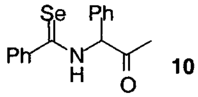
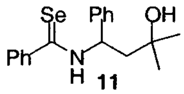
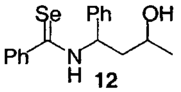
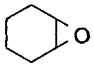
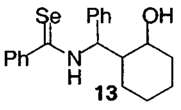
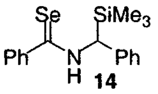


Table 1. Reaction of Dianion **3a** Generated from Selenoamide **1a** with Electrophiles[a]



entry	RX	product	yield [%][b]	^{77}Se NMR
1		 **7**	79	648.4
2		 **8**	66	662.6
3		 **9**	84	660.7
4		 **10**	54	608.3
5		 **11**	72	644.7
6		 **12**	95 (59 : 41)[c]	580.5[d] 645.1[e]
7		 **13**	72 (66 : 34)[c]	645.1[d] 575.6[e]
8	Me_3SiCl	 **14**	86	642.1

[a] The selenoamide **1** was treated with BuLi (2 equiv) at 0 °C for 0.5 h, and then the electrophile was added to the reaction mixture at 0 °C. [b] Isolated yield. [c] The diastereomer ratio is shown in parentheses. [d] For the major product. [e] For the minor product.

which gave *S*-ethyl thioimides **4b** and **5b** in high yields via thioamide monoanion **2b** and dianion **3b**, but the reaction of selenoamide **1a** showed better stereoselectivity. When the dianion **3a** was treated with 1 equiv of ethyl iodide, ethylation took place selectively at the carbon atom adjacent to the nitrogen atom of **3a**, and workup of the reaction mixture with water regenerated a selenocarbonyl group to give selenoamide **6** in good yield.[10]

To synthesize new types of selenoamides[11] via the dianion **3a**, various electrophiles were tested. The results are summarized in Table 1. As carbon electrophiles, cyclohexyl bromide, allylic bromides, acetyl chloride, and oxiranes were used to give the corresponding selenoamides in good to high yields as stable compounds (entries 1−7). The trimethylsilyl chloride underwent silylation of the dianion to give *N*-1-trimethylsilyl-1-phenylmethyl selenoamide **14** (entry 8). In the reaction of crotyl bromide, the substitution reaction took place at the carbon atom attached to the bromine atom, and the stereochemistry of the starting bromide was retained in the product **9** (entry 3). Ring opening of isobutyrene oxide and propylene oxide proceeded selectively at the primary carbon atom of their rings, although two diastereomers were formed in a nearly equal ratio in the latter case (entries 5 and 6). As for the reaction of cyclohexene oxide, two of four possible stereoisomers were obtained in a ratio of 66:34.

To identify the relative stereochemistry and structural features of the product **13**, X-ray structure analysis of the major diastereomer **13** was carried out.[12] The ORTEP

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[10] **Experimental Procedure.** In a 20-mL two-necked flask, to a THF solution (2 mL) of *N*-benzyl selenobenzamide (**1a**) (0.129 g, 0.47 mmol) was added butyllithium (0.61 mL, 0.97 mmol) at 0 °C, and the mixture was stirred at 0 °C for 0.5 h under a nitrogen atmosphere. Ethyl iodide (0.038 mL, 0.48 mmol) was then added to the reaction mixture at 0 °C, and stirring was continued at that temperature for 0.5 h. The reaction mixture was poured onto water and extracted with Et_2O (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/CH_2Cl_2 as an eluent to give 0.117 g (82%) of **6** as an orange oil. The product **6** could be stored in the refrigerator for more than 1 year.

[11] For recent examples of the syntheses of selenoamides, see: (a) Li, G. M.; Zingaro, R. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 647−650. (b) Li, G. M.; Zingaro, R. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, *136−138*, 525−530. (c) Ishihara, H.; Yosimura, K.; Kouketsu, M. *Chem. Lett.* **1998**, 1287−1288. (d) Koketsu, M.; Kanoh, M.; Itoh, E.; Ishihara, H. *J. Org. Chem.* **2001**, *66*, 4099−4101. (e) Ishihara, H.; Koketsu, M.; Fukuta, Y.; Nada, F. *J. Am. Chem. Soc.* **2001**, *123*, 8408−8409.

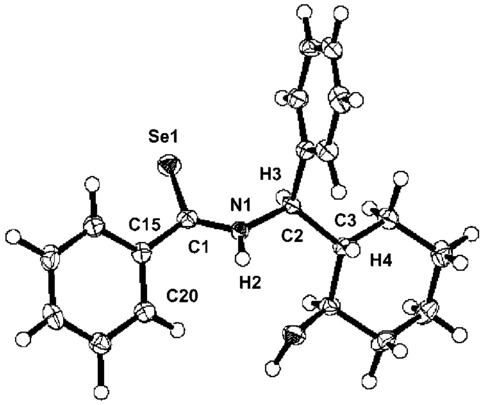

Figure 1. ORTEP drawing of **13**. Selected bond lengths (Å): Se1−C1, 1.834(3); N1−C2, 1.471(4); C1−N1, 1.325(4); C1−C15, 1.486(4). Selected bond angles (deg): Se1−C1−N1, 124.9(2); Se1−C1−C15, 119.3(2). Selected torsion angles (deg): Se1−C1−C15−C20, 127.2(3): Se1−C1−N1−C2, 4.0(4); H3−C2−C3−H4, 173; H2−N1−C2−H3, 153.

drawing of **13** is shown in Figure 1, along with the selected bond lengths, bond angles, and torsion angles. The results indicate that the relative configuration of three successive chiral carbon atoms in **13** is *R**,*S**,*R**.

On the basis of this result and NMR spectra, the relative configuration of the minor diastereomer **13** was also identified to be *S**,*R**,*S**. Ring opening of cyclohexene oxide with the dianion **3a** takes place with an inversion of configuration at the carbon atom next to the oxygen atom. The bond length in the C═Se group was 1.834(3) Å, which is close to the ordinary bond lengths of selenoamides.[13] The aromatic ring attached to the carbon atom of C═Se group deviated from the plane involving the C═Se group (Se1−C1−C15−C20 = 127.2(3)°). There was no interaction between the selenium atom and the hydrogen atom of the hydroxy group. This result was also supported by ^{77}Se NMR spectra (Table 1). The signal of the selenium atom of the major diastereomer **13** was observed at δ 645.1, which is similar to those seen for *N*-1-alkyl or 1-allyl-1-phenylmethyl selenoamides **7**−**9**. In contrast, the signal of the minor diastereomer **13** was shifted to a higher field, which may indicate intramolecular hydrogen bonding involving a C═Se···H−O group,[14] although further studies are necessary.

In summary, we have demonstrated the deprotonation of a selenoamide leading to a monoanion and dianion with high efficiency and selectivity. The synthesis of secondary selenoamides was attained by reacting the dianion with various electrophiles. Further studies on the synthetic reactions of heavy-atom-containing conjugate ions are in progress.

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Supporting Information Available: Spectroscopic data for **4a**, **5a**, and **6**−**14** and tables of crystallographic data for **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Crystal data for **13**: $C_{20}H_{23}NOSe$, FW = 372.37, triclinic, space group P1 (No. 2), a = 10.840(2) Å, b = 11.446(3) Å, c = 7.997(1) Å, β = 92.64(2)°, γ = 116.03, V = 850.2(4) Å^3, Z = 2, D_{calc} = 1.454 g·cm^{-3}, μ (Mo Kα) = 22.13 cm^{-1}, T = 193 K, R = 0.038, Rw = 0.039, 2921 reflections (I > 3 $\sigma(I)$), GOF = 1.65.

(13) (a) Murai, T.; Mizutani, T.; Kanda, T.; Kato, S. *Heteroatom Chem.* **1995**, *6*, 241−246. (b) Otten, P. A.; Gorter, S.; van der Gen, A. *Chem. Ber.* **1997**, *130*, 49−54. (f) Li, G. M.; Zingaro, R. A.; Segi, M.; Reibenspies, J. H.; Nakajima, T. *Organometallics* **1997**, *16*, 756−762. (g) Murai, T.; Niwa, N.; Ezaka, T.; Kato, S. *J. Org. Chem.* **1998**, *63*, 374−376. (h) Li, G. M. Reibenspies, J. H.; Derecskei-Kovacs, A.; Zingaro, R. A. *Polyhedron* **1999**, *18*, 3391−3399.

(14) Very recently, C−H···Se═C and N−H···Se═C interactions have been studied: (a) Wu, R.; Hernández, G.; Odom, J. D.; Dunlap, R. B.; Silks, L. A. *Chem. Commun.* **1996**, 1125−1126. (b) Wu, R.; Hernández, G.; Dunlap, R. B.; Odom, J. D.; Martinez, R. A.; Silks, L. A. *Trends. Org. Chem.* **1998**, *7*, 105−114. (c) Li, Z.; Wu, R.; Michalczyk, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A. *J. Am. Chem. Soc.* **2000**, *122*, 386. (d) Michalczyk, R.; Schmidt, J. G.; Moody, E.; Li, Z.; Wu, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3067−3070.