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Selenoimidoylation of Alcohols with Selenium and Isocyanides and Its Application to the Synthesis of Selenium-Containing Heterocycles

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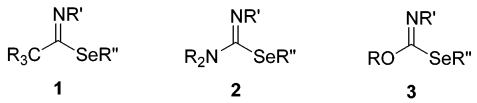
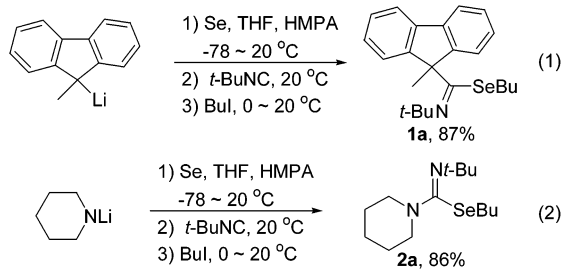
Abstract: The reaction of alcohols with selenium and isocyanides in the presence of DBU gave oxyimidoylselenoates **6**. Trapping of **6** with BuI resulted in high-yield formation of selenocarbonimidates **4**. When alk-2-yn-1-ols **9** were allowed to react with selenium and isocyanides under similar conditions, new selenium-containing heterocycles **10**, 2-imino-4-alkylidene-1,3-oxaselenolanes, were obtained via cycloaddition of oxyimidoylselenoates **13** generated in situ by intramolecular addition of selenolates to carbon−carbon triple bonds.

Organoselenium compounds have been recognized not only as useful intermediates in synthetic chemistry[1] but also as important materials in biological and medicinal chemistry.[2] As for the compounds containing a selenoimidoyl skeleton (Se−C═N), selenoimidates **1** have been synthesized and used as precursors of imidoyl radicals[3] and iminoethers.[4] Isoselenoureas **2** have been employed for the generation of selenolate anions under mild conditions by treatment with bases such as NaOH and Bu_4NOH;[5] however, selenocarbonimidate **3** has never been prepared. We now report a high-yield selenoimidoylation method of alcohols with isocyanides and elemental selenium under mild conditions.



1 **2** **3**

Previously described methods for the preparation of selenoimidates **1** are (i) alkylation of selenoamides with alkyl halides,[6] (ii) reaction of imidoyl chlorides with selenols,[7] (iii) reaction of imidoyl radicals with diaryl diselenides,[8] (iv) three-component radical coupling reactions of diselenides with isocyanides and alkynes,[9] (v) transition-metal-catalyzed addition of diaryl diselenide to isocyanide,[10] and (vi) reaction of oxime sulfonates with organoaluminum selenolates.[4] Isoselenoureas **2** can also be prepared by the reaction of selenoureas with alkyl halides[11,5a,d,e,g,h] or an alkyl sulfate.[12]



We have recently shown that the reaction of benzyllithiums or lithium amides with selenium and isocyanides provides the corresponding selenoimidates **1** (eq 1) or isoselenoureas **2** (eq 2), respectively, in high yields after trapping with alkyl iodide electrophiles.[13,14]

Similarly, we have also reported that benzyllithiums react readily with isoselenocyanates at low temperatures

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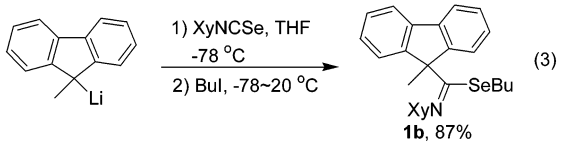
TABLE 1. Syntheses of Selenocarbonimidates[a]

run	R^1	R^2	product	yield[d] (%)
1	Me	*c*-Hex[b]	**4a**	92
2	Me	Xy[c]	**4b**	85
3	Bu	*c*-Hex	**4c**	64
4	Bu	Xy	**4d**	82
5	*s*-Bu	Xy	**4e**	45
6	*t*-Bu	Xy	**4f**	0
7	Allyl	*c*-Hex	**4g**	76
8	Bn	*c*-Hex	**4h**	94
9	Bn	Xy	**4i**	86

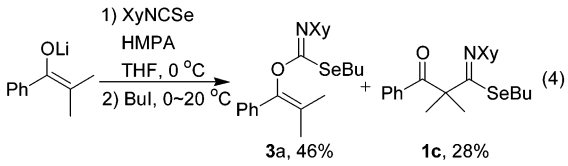
[a] Conditions: Se (1 mmol), alcohol (2 mmol), isocyanide (1 mmol), DBU (1 mmol), THF (1 mL) rt, 20 h, then BuI (2 mmol), 1 h. [b] Cyclohexyl. [c] 2,6-Xylyl. [d] Isolated yields based on Se used.

to give selenoimidates **1** in high yields after trapping with alkyl iodides (eq 3).[15]



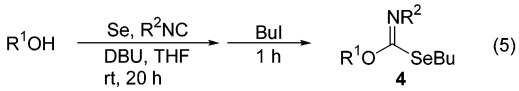
(3)

Aiming at the synthesis of selenocarbonimidates **3**, we attempted the reaction of 2,6-xylyl isoselenocyanate with a lithium enolate of propiophenone under the conditions shown in eq 3; however, no reaction took place. The first example of the synthesis of selenocarbonimidate was realized by carrying out a similar reaction in the presence of HMPA at 0 °C to afford **3a** in 46% yield together with selenoimidates **1c** (eq 4).[15]



(4)

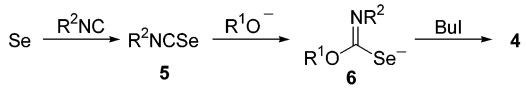
To develop a more convenient synthetic procedure, we stirred a mixture of methanol (2 mmol), cyclohexyl isocyanide (1 mmol), and selenium (1 mmol) in THF (1 mL) in the presence of DBU (1 mmol) at room temperature. The black suspension became a yellow homogeneous solution within 3 h. Quenching the reaction with BuI after 20 h and subsequent workup afforded the expected selenocarbonimidate **4a** in 92% yield based on selenium used (eq 5).



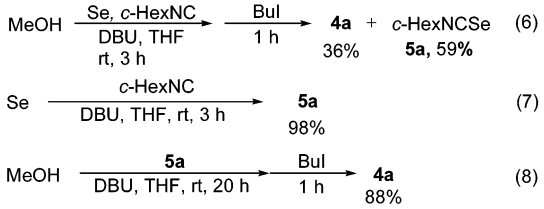
(5)

Results of the reactions performed using several alcohols are summarized in Table 1.[16] Both aliphatic and aromatic isocyanides were applicable to the present reaction. Primary alcohols such as *n*-butanol, allyl alcohol, and benzyl alcohol provided the corresponding selenocarbonimidates **4c**−**d**,**g**−**i** in good to excellent yields under similar conditions. *sec*-Butanol, however, gave **4e** in lower yield and *tert*-butyl alcohol did not provide selenocarbonimidate **4f**, probably due to steric reasons. All selenocarbonimidates shown in Table 1 could easily be isolated as single stereoisomers.[17]

SCHEME 1. Plausible Reaction Pathway

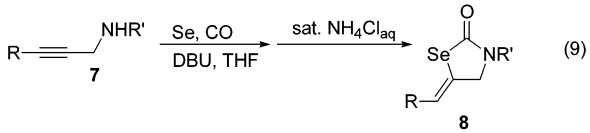


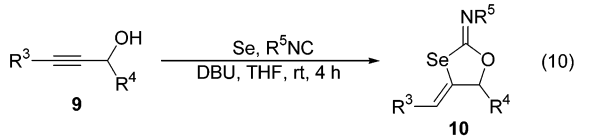
We carried out the following control experiments in order to examine the reaction pathways. Under the conditions indicated in Table 1, cyclohexyl isocyanide reacted with selenium and methanol to afford **4a** in 92% yield. When the reaction time was shortened from 20 to 3 h, **4a** was formed in 36% yield together with 59% of cyclohexyl isoselenocyanate **5a** (eq 6). Next, the reaction of selenium with cyclohexyl isocyanide in the presence of DBU for 3 h resulted in the formation of **5a** in 98% (eq 7).[18] Finally, **5a** reacted with methanol in the presence of DBU to give **4a** in 88% yield (eq 8).



By combining these steps, we propose the reaction pathway shown in Scheme 1. Isocyanide react with selenium to give the corresponding isoselenocyanate **5**. Alkoxide attack at the carbon center of **5** produces oxyimidoylselenoate **6**, which is trapped by BuI to yield selenocarbonimidate **4**.

We recently reported that 1-amino-2-alkynes **7** reacted with selenium and carbon monoxide in the presence of DBU to yield 5-alkylideneselenazolin-2-ones **8** stereoselectively (eq 9).[19] We then attempted to apply this principle to the preparation of 4-alkylidene-1,3-oxaselenolanes **10** from alk-2-yn-1-ols **9**, selenium, and isocyanides (eq 10).





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(16) Selenocarbonimidate **4b** was also obtained in 72% yield when the reaction was carried out under conditions similar to those shown in eqs 1 and 2 by starting with MeOLi.

(17) Low-temperature ^{1}H NMR of **4b** showed a set of peaks assignable to a single isomer. However, we could not determine the stereochemistry of the carbon−nitrogen double bond because a nuclear Overhauser effect was not observed when we irradiated methyl protons of 2,6-xylyl group in **4b**.

(18) Triethylamine promoted the reaction of selenium with isocyanides to yield isoselenocyanates; see: Sonoda, N.; Yamamoto, G.; Tsutsumi, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2937.

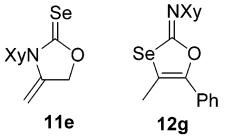
TABLE 2. Synthesis of Selenium-containing Heterocycles from 9[a]

run	substrate	R^3	R^4	R^5	product	yield (%)
1	**9a**	Ph	H	Xy	**10a**	92
2	**9b**	*p*-MeC_6H_4	H	Xy	**10b**	88
3	**9c**	*p*-$MeOC_6H_4$	H	Xy	**10c**	91
4	**9d**	*p*-ClC_6H_4	H	Xy	**10d**	96
5	**9e**	H	H	Xy	**10e**	69[b]
6	**9f**	Me	H	Xy	**10f**	85[c] (13)
7	**9g**	H	Ph	Xy	**12g**	68
8	**9a**	Ph	H	*c*-Hex	**10h**	85

[a] Conditions: Se (1 mmol), isocyanide (1 mmol), alk-2-yn-1-ol **9** (1 mmol), DBU (1 mmol), THF (1 mL), rt, 4 h. [b] **11e** was also obtained (21%). [c] With CuI (1 mmol).

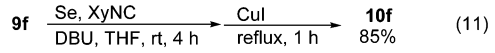
3-Phenyl-2-propyn-1-ol **9a** (1 mmol) was allowed to react with selenium (1 mmol) and 2,6-xylyl isocyanide (1 mmol) in the presence of DBU (1 mmol) in THF (1 mL) at room temperature for 4 h. Purification of the reaction mixture by silica gel column chromatography provided 2-imino-4-alkylidene-1,3-oxaselenolane **10a** in 92% yield (run 1 of Table 2).

When *p*-methyl-, *p*-methoxy-, or *p*-chlorophenyl propargylic alcohols were employed, the expected products **10b**−**d** were also obtained in high yields. Prop-2-yn-1-ol **9e** gave **10e** in 69% yield along with 21% of its isomer **11e**.



11e **12g**

The reaction of but-2-yn-1-ol **9f** afforded **10f** in only 13% yield. Since it is known that CuI promotes the intramolecular cyclization of *O*-propargyl thiocarbonates[20] and *N*-propargyl selenocarbamates,[19] we added 1 equiv of CuI to the resulting mixture of the reaction of **9f** with 2,6-xylyl isocyanide and selenium and heated the mixture at reflux for 1 h. This procedure led to efficient production of **10f** in 85% yield (eq 11, run 6).

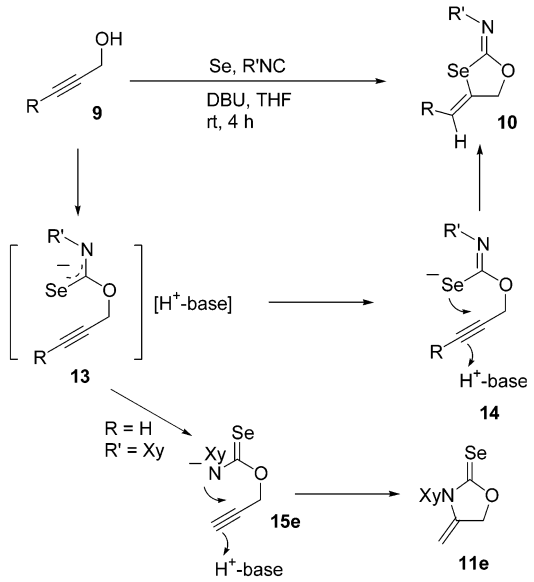


(11)

Propargyl alcohol having a phenyl group at the α-carbon **9g** underwent selenoimidoylation to give a cyclized product in 68% yield; however, the product isolated was 2-imino-1,3-oxaselenole **12g** rather than the exomethylene isomer **10g**.[21] It should be noted that all 2-imino-4-alkylidene-1,3-oxaselenolanes obtained (**10a**−**f**,**h**) adopt a single configuration with respect to carbon−carbon and carbon−nitrogen double bonds. In the case of **10a**, *Z*-configurations of the carbon−carbon and carbon−nitrogen double bonds were determined by X-ray analysis.

A reaction mechanism for this transformation is suggested in Scheme 2. First, alk-2-yn-1-ol **9** undergoes

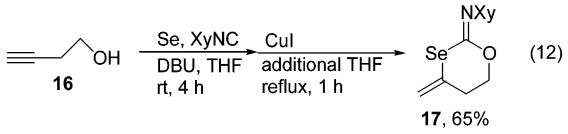
SCHEME 2. Reaction Pathway for the Formation of *Z*-Imino-4-alkylidene-1,3-dioxaselenolanes



selenoimidoylation by the reaction with selenium and isocyanide to yield oxyimidoylselenoate **13**. The stereoselectivity of the C═C double bonds of the products can be explained by a trans addition mechanism (**13** → **14** → **10**), where proton coordination to the carbon−carbon triple bond facilitates nucleophilic addition of selenium to the triple bond from the opposite site. 2-Selenoxo-1,3-oxolidine **11e** is formed by the nucleophilic addition of nitrogen to the carbon−carbon triple bond of **13**.[22]

When the reaction of but-3-yn-1-ol **16** was conducted under similar conditions as eq 10 and Table 2, the expected six-membered heterocycle **17**, 4-methylidene-1,3-selenane, was not formed at all. However, addition of CuI and subsequent heating of the reaction mixture at reflux afforded **17** in 41% yield.

Finally, the yield was boosted to 65% by diluting the reaction mixture with 9 mL of additional THF before addition of CuI (eq 12).



(12)

In summary, alcohols were selenoimidoylated with selenium and isocyanides under mild conditions to give selenocarbonimidates **4** after trapping with BuI. Furthermore, the reaction of alk-2-yn-1-ols **9** with selenium and isocyanides produced oxyimidoylselenoates **13**, which underwent intramolecular cycloaddition affording new selenium-containing heterocycles **10**.

Experimental Section

THF was distilled from sodium benzophenone ketyl. Methanol, butanol, *sec*-butanol, *tert*-butyl alcohol, allyl alcohol, benzyl alcohol, BuI, and DBU were distilled from calcium hydride. Alk-

(19) Fujiwara, S.; Shikano, Y.; Shin-ike, T.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **2002**, *67*, 6275.

(20) Mizuno, T.; Nakamura, F.; Ishino, Y.; Nishiguchi, I.; Hirashima, T.; Ogawa, A.; Kambe, N.; Sonoda, N. *Synthesis* **1989**, 770.

(21) A few 2-imino-1,3-oxaselenoles have been synthesized, see: (a) Robert, A.; Marechal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 447. (b) Maréchal, A. M. L.; Robert, A.; Leban, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 351.

(22) The product selectivity observed is due to higher nucleophilicity of the selenium atom. In fact, the product ratio was almost the same when the reaction time was shortened to 1 h. Isolated **10e** and **11e** were not interconverted under similar reaction conditions.

2-yn-1-ols **9a**,**e**,**f**,**g**, but-3-yn-1-ol, and cyclohexyl isocyanide were purchased and used without further purification. Other alk-2-yn-1-ols **9b**−**d** were synthesized by the reaction of propargyl alcohol with the corresponding aryl iodides.[23] 2,6-Xylyl isocyanide was prepared from 2,6-xylidine via 2,6-xylyl formamide.[24]

1-Methyl-2-butyl-3-cyclohexylselenocarbonimidate (4a): Typical Experimental Procedure. Into a 5-mL flask were added selenium (1.0 mmol, 79.5 mg), DBU (1 mmol, 161.8 mg), THF (1 mL), cyclohexyl isocyanide (1 mmol, 115.7 mg), and methanol (2.1 mmol, 70.5 mg) at room temperature, and the mixture was stirred for 20 h. BuI (2 mmol, 365.2 mg) was then added, and stirring was continued for an additional 1 h at room temperature. *n*-Hexane was added, and the deposited white solids were removed by filtration. The filtrate was concentrated in vacuo and purified by preparative HPLC eluted with $CHCl_3$ to give 1-methyl-2-butyl-3-cyclohexylselenocarbonimidate **4a** as a yellow liquid (225.0 mg, 92% based on selenium used): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3 H), 1.17−1.45 (m, 7 H), 1.58−1.75 (m, 7 H), 2.95 (t, J = 7.4 Hz, 2 H), 3.05−3.11 (m, 1 H), 3.77 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 23.0, 24.9, 25.1, 25.9, 33.3, 34.3, 55.6, 60.2, 149.4; IR (NaCl) 1652 (C═N) cm^{-1}; MS (EI) *m*/*z* (relative intensity) 277 (M^+, 2). Anal. Calcd for $C_{12}H_{23}NOSe$: C, 52.17; H, 8.39; N, 5.07. Found: C, 51.98; H, 8.31; N, 5.26.

(23) **9b,d** were prepared by modified reactions of the general procedure for synthesis of aryl alkynes reported in the following paper; Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412.

(24) Conversion of 2,6-xylidine to 2,6-xylyl formamide, see: Krishnamurthy, S. *Tetrahedron Lett.* **1982**, *23*, 3315. Dehydration of 2,6-xylyl formamide to 2,6-xylyl isocyanide, see: Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, 400.

2-(2,6-Xylyl)imino-4-phenylmethylidene-1,3-oxaselenolane (10a): Typical Experimental Procedure. Into a 5-mL flask was placed selenium (1.0 mmol, 78.0 mg), DBU (1 mmol, 163.9 mg), THF (1 mL), 2,6-xylyl isocyanide (1 mmol, 140.4 mg), and 3-phenyl-2-propyn-1-ol (1 mmol, 140.2 mg), and the mixture was stirred for 4 h at 20 °C. Saturated NH_4Cl (aq) (1 mL) was then added and the stirring continued for an additional 0.5 h. The mixture was concentrated and purified by silica gel column chromatography to yield **10a** as white solid (321.6 mg, 92% based on Se used): mp 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 6 H), 5.20 (d, J = 0.8 Hz, 2H), 6.93−7.33 (m, 9 H); NOE experiment, irradiation of methylene at δ 5.20 resulted in 10% enhancement of signal at δ 6.93 (vinyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 78.0, 123.6, 124.1, 127.5, 127.7, 128.1, 128.5, 128.7, 131.3, 135.6, 146.8, 160.7; IR (KBr) 1672 (C═N) cm^{-1}; MS (EI) *m*/*z* (relative intensity) 343 (M^+, 19). Anal. Calcd for $C_{18}H_{17}NOSe$: C, 63.16; H, 5.01; N, 4.09. Found: C, 62.87; H, 5.28; N, 4.19.

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Supporting Information Available: Detailed characterization data of all new compounds and an ORTEP diagram and X-ray structure data for compound **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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