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MeOTf-Mediated Alkynylation of Selenoamides Leading to *β*-Methylselenenyl α,*β*-Unsaturated Ketones and Their Characterization

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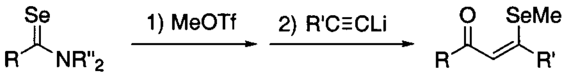
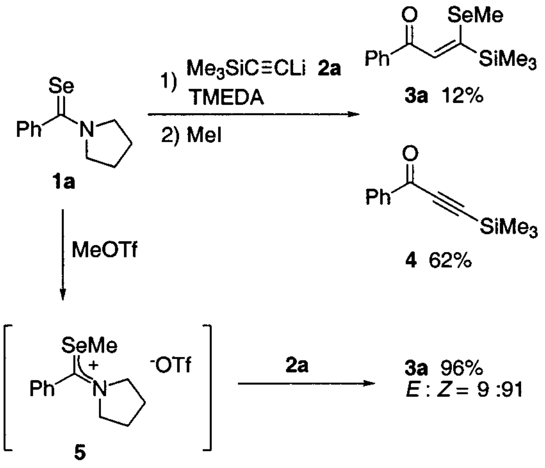
ABSTRACT



β-Methylselenenyl α,β-unsaturated ketones were effectively synthesized by treating selenoamides with methyl triflate, followed by reaction with lithium acetylides. The reaction proceeded with high stereoselectivity to give exclusively *Z*-isomers. ^{77}Se NMR studies and X-ray molecular structure analysis of β-methylselenenyl α,β-unsaturated ketones suggested that the products show 1,5-nonbonding interaction between the selenium atom and carbonyl oxygen atom.

Considerable attention has been paid to the chemistry of organoselenium compounds because of their value as synthetic reagents[1] and their possible biological application.[2] In the course of our studies on selenocarbonyl compounds,[3] we previously reported efficient methods for the synthesis of aliphatic selenoamides[4] and the conversion of α,α-disubstituted selenoamides with organolithium reagents to asymmetrical ketones.[5] We further found that the reaction of selenoamides with lithium acetylide derived from (trimethylsilyl)acetylene and methyl iodide gives β-methylselenenyl α,β-unsaturated ketones.[5] However, only a limited number of lithium acetylides and selenoamides were suitable for this transformation. We describe here the efficient synthesis of β-methylselenenyl α,β-unsaturated ketones by the MeOTf-mediated reaction of selenoamides with lithium acetylides. The β-methylselenenyl α,β-unsaturated ketones were characterized by ^{77}Se NMR spectra and X-ray molecular structure analysis.

Scheme 1



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[1] Krief, A. In *Comprehensive Organometallic Chemistry*; Abel, W. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 11, pp 515−569. Back, T. G., Ed. *Organoselenium Chemistry: A Practical Approach*; Oxford University Press: U.K., 1999.

[2] El-Bayoumy, K. *Drugs Fut.* **1997**, *22*, 539−545.

[3] Murai, T.; Kato, S. In *Topics in Current Chemistry*; Wirth, T., Ed.; Springer-Verlag: Berlin, 2000; Vol. 208, pp 177−199 and references therein.

[4] Murai, T.; Ezaka, T.; Niwa, N.; Kanda, T.; Kato, S. *Synlett* **1996**, 865−866. Murai, T.; Ezaka, T.; Kanda, T.; Kato, S. *J. Chem. Soc., Chem. Commun.* **1996**, 1809−1810. Murai, T. Ezaka, T.; Ichimiya, T.; Kato, S. *Synlett* **1997**, 775−776. Murai, T.; Mori, T.; Kato, S. *Synlett* **1998**, 619−620. Murai, T.; Ezaka, T.; Kato, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1193−1200. Murai, T.; Suzuki, A.; Ezaka, T.; Kato, S. *Org. Lett.* **2000**, *2*, 311−313.

[5] Murai, T.; Ezaka, T.; Kato, S. *Tetrahedron Lett.* **1998**, *39*, 4329−4332.

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Initially, the aromatic selenoamide **1a**[6] was reacted with lithium acetylide **2a** derived from (trimethylsilyl)acetylene at 0 °C to room temperature for 1.5 h, and then methyl iodide was added to the reaction mixture as described previously.[5] As a result, alkynyl ketone **4** was obtained in 62% yield along with a small amount of β-methylselenenyl α,β-unsaturated ketone **3a** (Scheme 1). After several disappointing results in the selective synthesis of ketone **3a**, treatment of selenoamide **1a** with methyl trifluoromethanesulfonate (methyl triflate) prior to the reaction with lithium acetylide **2a** gave ketone **3a** in 96% yield[7,8] with *Z*-stereoselectivity.

This new procedure leading to **3a** allowed for the use of various selenoamides **1** and lithium acetylides **2** (Scheme 2). The results are summarized in Table 1. As the selenoamide, aromatic selenoamides **1a**–**1c**, selenoacetamide **1d**, and α-mono- and α,α-disubstituted selenoamides **1e**–**1h** were used. In almost all cases, the reaction proceeded smoothly at room temperature and was complete within 3 h to afford *Z*-isomers of β-methylselenenyl α,β-unsaturated ketones **3** as major products.[9] In the reaction of aromatic selenoamides bearing a methoxy group and bromine atom, **1b** and **1c** did not affect the yields of the products **3c** and **3d** (entries 2 and 3). The reaction with lithium acetylides **2c** and **2e** derived from phenylacetylene and 1-hexyne gave the products **3** in moderate to good yields (entries 4, 5, 8, and

Scheme 2

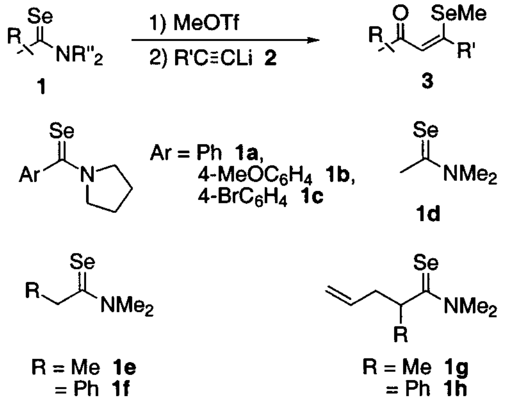
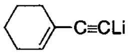
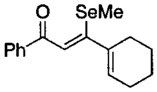
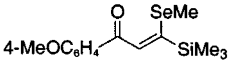
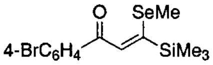
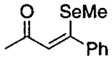
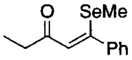
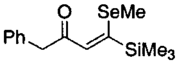
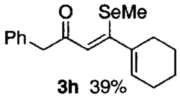
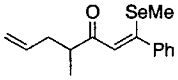
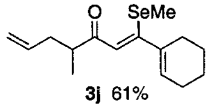
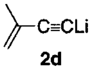
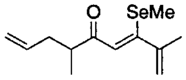
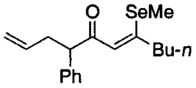
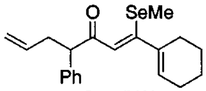
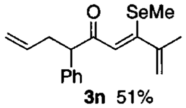


Table 1. Reaction of Selenoamides with Lithium Acetylides[a]

entry	seleno-amide **1**	R'C≡CLi **2**	product yield (%)[b]
1	**1a**	 **2b**	 **3b** 50%
2	**1b**	**2a**	 **3c** 72%
3	**1c**	**2a**	 **3d** 64%
4[c]	**1d**	PhC≡CLi **2c**	 **3e** 83% *E* : *Z* = 38 : 62
5[c]	**1e**	**2c**	 **3f** 70% *E* : *Z* = 13 :87
6[c]	**1f**	**2a**	 **3g** 54% *E* : *Z* = 52 :48
7[c]	**1f**	**2b**	 **3h** 39%
8[d]	**1g**	**2c**	 **3i** 88%
9[d]	**1g**	**2b**	 **3j** 61%
10[d]	**1g**	 **2d**	 **3k** 39%
11[d]	**1h**	*n*-BuC≡CLi **2e**	 **3l** 53%
12[d]	**1h**	**2b**	 **3m** 74%
13[d]	**1h**	**2d**	 **3n** 51%

[a] The selenoamide **1** (1 mmol) was treated with methyl triflate (1 mmol) in Et_2O (5 mL) at 0 °C for 30 s. Then, to the reaction mixture was added an Et_2O solution of the lithium acetylide **2** (3 mmol), and the solution was stirred for 1.5 h. [b] Isolated yield. [c] The reaction mixture was stirred for 0.5 h. [d] The reaction mixture was stirred for 3 h.

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(6) Li, G. M.; Zingaro, R. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 647–650.

(7) **Experimental procedure**: To an Et_2O solution of 1-(1-phenyl-1-selenoxomethyl)pyrrolidine (**1a**) (0.238 g, 1 mmol) was added methyl triflate (0.115 mL, 1 mmol) at room temperature, and the mixture was stirred for 30 s at this temperature. To this was added an Et_2O solution (5 mL) of lithium acetylide **2a** prepared from (trimethylsilyl)acetylene (0.42 mL, 3 mmol) and BuLi (1.6 M hexane solution, 1.88 mL, 3 mmol) at 0 °C, and this was stirred for 1.5 h at room temperature. The resulting mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane:CH_2Cl_2 = 1:1) to give **3a** (0.286 g, 0.96 mmol) in 96% yield.

(8) Preliminary ^{77}Se NMR studies have indicated a change in the chemical shift from 717.6 ppm, corresponding to selenoamide **1a**, to 442.5 ppm upon the addition of methyl triflate to a $CDCl_3$ solution of **1a**. Thus, methylselenenyl iminium ion **5** may be formed in the initial stage of the reaction.

(9) The stereochemistry of some of the products was determined by phase-sensitive NOESY spectroscopy, and that of others was estimated on the basis of the similarities in ^1H and ^{13}C NMR spectra.

11). However, in the reaction with lithium acetylides **2b** and **2d** derived from enynes, the yields of the products depended on the starting selenoamides **1** (entries 1, 7, 9, 10, 12, and 13), probably because of the stability of α,β,γ,δ-unsaturated ketones **3**.[10] The reaction of aromatic selenoamide **1a** and α,α-disubstituted selenoamides **1g** and **1h** with lithium acetylide **2b** gave the corresponding products in 50−74% yields (entries 1, 9, and 12), whereas the reaction of α-monosubstituted selenoamide **1f** gave the product **3h** in 39% yield (entry 7). Furthermore, the desired products were not obtained from the reaction of selenoamides **1d** and **1e** with lithium acetylide **2b**.

The β-methylselenenyl α,β-unsaturated ketones **3** were characterized by ^{77}Se NMR spectra, as shown in Table 2.

Table 2. ^{77}Se-NMR Spectra of α,β-Unsaturated Ketones **3**

		^{77}Se-NMR ($CDCl_3$) δ (ppm)	
entry	compound **3**	*Z*-isomer	*E*-isomer
1	**3a**	419.6	310.5
2	**3e**	372.6	306.4
3	**3f**	369.4	304.2
4	**3g**	413.1	300.1

The signals of *Z*-isomers of **3** were in a lower region than those of *E*-isomers of **3**. The results in Table 2 suggest that the selenium atoms of *Z*- and *E*-isomers of **3** are in a different electronic environment.[11] To elucidate the structural features of the products **3**, an X-ray molecular structure analysis of β-methylselenenyl α,β-unsaturated ketone **3b** was carried out. This confirmed that the product **3b** had a *Z*-configuration (Figure 1).[12] The intramolecular distance between the selenium atom and the oxygen atom of the carbonyl group was 2.74(8) Å and was within the sum of the van der Waals radii of both atoms.[13] Accordingly, 1,5-nonbonding intramolecular interaction between these two atoms is present.[14] Additionally, the dihedral angle formed by the α,β-unsaturated carbonyl unit and the cyclohexenyl plane is almost a right angle (87.4(7)°).

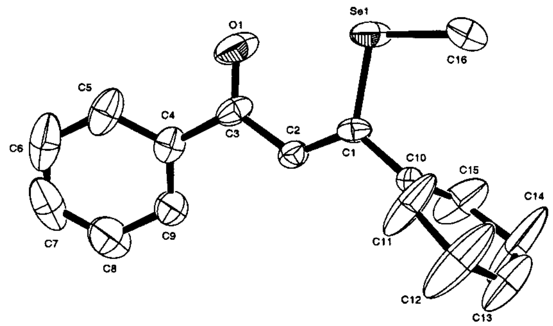

Figure 1. Ortep drawing of **3b**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Se1−C1, 1.892(4); Se1−C16, 1.939(7); O1−C3, 1.217(5); C10−C15, 1.408(8); C10−C11, 1.345(7). Selected torsion angles (deg): Se1−C1−C10−C11, 91.8(6); Se1−C1−C2−C3, −2.5(7); O1−C3−C2−C1, −0.7(8); O1−C3−C4−C5−26.8(7).

In summary, we have demonstrated a highly efficient conversion of selenoamides to β-methylselenenyl α,β-unsaturated ketones by the MeOTf-mediated reaction with lithium acetylides. Further studies should focus on the synthetic application of the present reactions and elucidation of their reaction pathways, which should involve several types of new chemical species.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Spectroscopic data of **3** and tables of crystallographic data including atomic positional and thermal parameters for **3b**. This material is available free of charge via the Internet at http://pubs/acs/org.

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[10] The introduction of a methylselenenyl group to the β-position of α,β,γ,δ-unsaturated ketones may reduce their stability, since various α,β,γ,δ-unsaturated ketones have been isolated in pure form: Ahlbrecht, H.; Ibe, M. *Synthesis* **1988**, 210−211. Herscovici, J.; Bounamaiza, L.; Antonakis, K. *Tetrahedron Lett.* **1991**, *32*, 1791−1794. Wei, X.; Taylor, R. J. K. *J. Org. Chem.* **2000**, *65*, 616−620. Matsubara, Y.; Yoshimatsu, M. *J. Org. Chem.* **2000**, *65*, 4456−4459.

[11] ^{77}Se NMR spectra are well-known to be highly sensitive to the electronic environment, see: Duddeck, H. *Prog. NMR Spectrosc.* **1995**, *27*, 1−323. Klapötke, T. M.; Broschag, M. *Compilation of Reported ^{77}Se NMR Chemical Shifts*; John Wiley & Sons: New York, 1996. Wu, R.; Silks, L. A.; Odom, J. D.; Dunlap, R. B. *Spectroscopy* **1996**, *11*, 37−42. Nakanishi, W.; Hayashi, S. *J. Phys. Chem. A* **1999**, *103*, 6074−6081. Poleschner, H.; Heydenreich, M.; Radeglia, R. *Magn. Reson. Chem.* **1999**, *37*, 333−345.

[12] Crystal data of **3b**: $C_{16}H_{18}NSe$, FW = 305.28, monoclinic, space group $P2_1/c$ (No. 14), a = 6.172(3) Å, b = 8.825(2) Å, c = 26.162(2) Å, β = 95.81(1)°, V = 1417.6(6) Å^3, Z = 4, D_{calcd} = 1.430 g·cm^{-3}, μ(Mo Kα) = 26.35 cm^{-1}, T = 193 K, F(000) = 624 R = 0.110, R_w = 0.146, R1 = 0.057, 3236 reflections ($I > -10.00\sigma(I)$), GOF = 1.24. The position of cyclohexenyl group is disordered: the olefinic unit should appear either between C10 and C11 or between C10 and C15.

[13] Sum of the van der Waals radii (Å): Se···O 3.50 Å: Nyburg, S. C.; Faerman, C. H. *Acta Crystallogr.* **1985**, *B41*, 274−279.

[14] Increasing attention has been paid to theoretical and experimental studies on 1,5-nonbonding interaction between an oxygen atom and chalcogen atoms because this is believed to play an important role in defining the molecular geometry, see: Mnyeav, R. M.; Minkin, V. I. *Can. J. Chem.* **1998**, *76*, 776−788. Nagao, Y.; Hirata, T.; Goto, S.; Sano, S.; Kakehi, A.; Iizuka, K.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 3104−3110. Komatsu, H.; Iwaoka, M.; Tomoda, S. *Chem. Commun.* **1999**, 205−206. Niyomura, O.; Kato, S.; Inagaki, S. *J. Am. Chem. Soc.* **2000**, *122*, 2132−2133.