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Reactions of α,α-disubstituted selenoamides with organolithium reagents leading to unsymmetrical ketones

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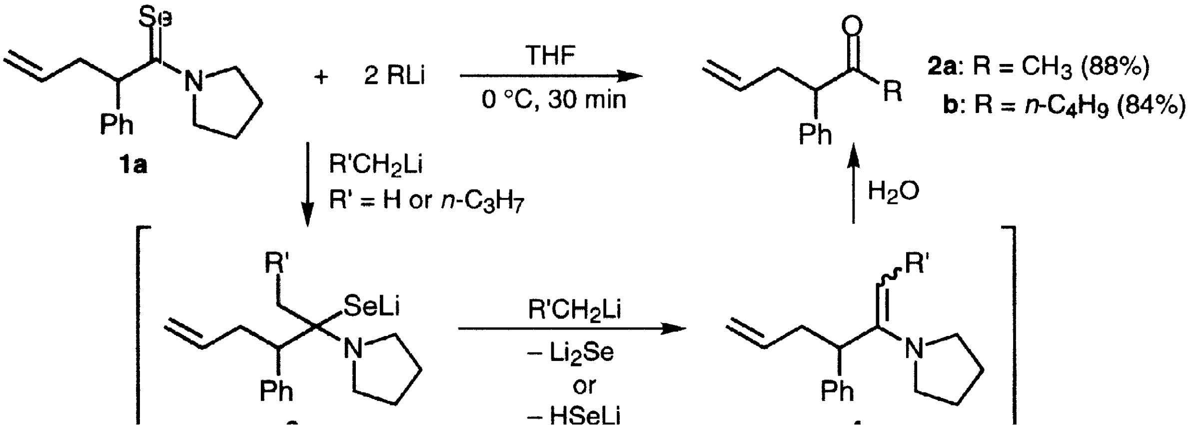
Abstract: α,α-Disubstituted selenoamides were easily converted to unsymmetrical ketones in high yields by the reaction with alkyllithiums, whereas the reaction with alkynyllithium and methyl iodide gave α,β-unsaturated ketone and dialkynylamine. © 1998 Elsevier Science Ltd. All rights reserved.

Keyword: selenium and compounds; alkylations; enamines

Organoselenium compounds have been widely studied in organic synthesis over the past twenty years.[1] For example, the importance of arylselenenyl groups (ArSe-) in organic synthesis has become increasingly clear.[1] In contrast, new reactions using selenocarbonyl compounds (C=Se) have been studied to a much lesser extent. In particular, the application of such reactions to synthetically available carbon-carbon bond-forming reactions with liberation of the selenium atom has not yet been reported except for the synthesis of hindered olefins from selenoketones.[2] In our studies on selenocarbonyl compounds, we recently reported new methods for synthesizing selenoamides.[3] We report here reactions of α,α-disubstituted selenoamides with organolithium reagents leading to unsymmetrical ketones.



Scheme 1

To a THF solution of the α,α-disubstituted selenoamide **1a**[3c] was added 2 equiv. of methyllithium at 0 °C, and the mixture was stirred at this temperature for 30 min (Scheme

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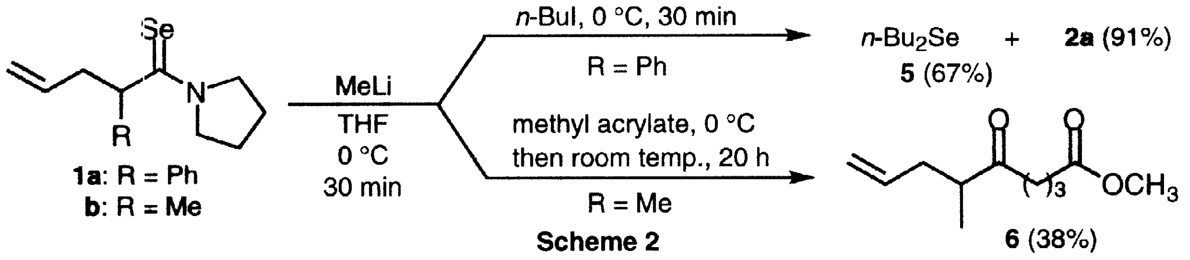
1). Aqueous workup of the mixture gave the unsymmetrical ketone **2a** in an isolated yield of 88% after column chromatography on silica gel. Similarly, the use of butyllithium gave ketone **2b** with equal efficiency. In these reactions, deprotonation at the α-position to the selenocarbonyl group of **1a** did not occur. ^{1}H and ^{13}C NMR spectra of the crude mixture of selenoamide **1a** and 2 equiv. of methyllithium showed the formation of an enamine **4** (R' = H) as an intermediate.[4,7] Accordingly, the ketones **2a**,**b** may be produced by the hydrolysis of enamines **4**, generated by the formal elimination of HSeLi from tetrahedral intermediates **3**. The addition of 2 equiv. of butyl iodide prior to aqueous workup of the reaction mixture of selenoamide **1a** and 2 equiv. of methyllithium gave dibutyl selenide **5** in good yield (Scheme 2). This result supports the formation of lithium selenides (HSeLi and/or Li_2Se) in the reaction of **1a** with alkyllithiums. The formation of enamine intermediates was further confirmed by treatment of the reaction mixture of selenoamide **1b** and 2 equiv. of methyllithium with 5 equiv. of methyl acrylate (Scheme 2).[8] The 1,5-dicarbonyl compound **6** was obtained as a product, although in moderate yield. The reaction pathway shown in Scheme 1 is in marked contrast to alkylations of ordinary amides such as Weinreb amides leading to ketones where tetrahedral intermediates similar to **3** are stable but break down upon aqueous workup.[9]



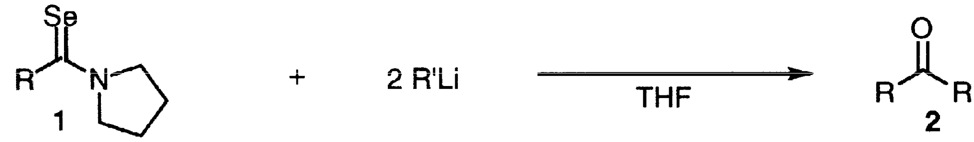
Scheme 2

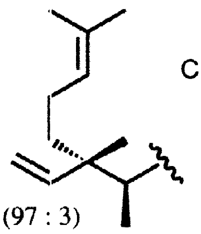
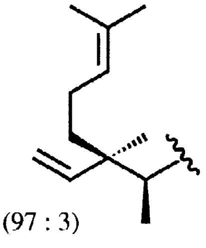
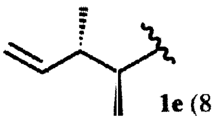
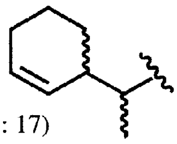
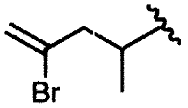
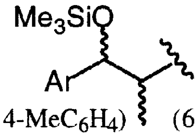
To establish the versatility of the reaction in Scheme 1, a range of selenoamides **1**[10] were subjected to alkylations with organolithium reagents.[11] The results are listed in Table 1. Conversion of selenoamides **1** to unsymmetrical ketones **2** with methyl- or butyl-lithium was complete within 30 min. Note that the ketones **2c–g**, which are not regioselectively accessible by reacting monosubstituted ketones with bases and allylic halides, were obtained from selenoamides **1c–g** with high purity.[12] The stereochemistry of the selenoamides **1c**,**d** was retained during the reaction to give the diastereoisomers **2c**,**d**, respectively (entries 1 and 2). The bromine atom attached to a vinyl carbon atom did not affect the reaction course even though a lithium-bromine exchange reaction[13] can take place at temperatures lower than that in the present reaction (entry 5). The β-siloxy group of **1h** remained intact under the reaction conditions to give the ketone **2h** in good yield (entry 6).

Reactions of selenoamides with alkynyllithium **7** were also examined (Scheme 3). The reaction of the selenoamide **1b** with 2 equiv. of **7** and methyl iodide gave the product **9**, in which two alkynyl groups were incorporated, along with a small amount of the α,β-unsaturated ketone **8**.[14] The selective formation of **8** was achieved by the use of 1 equiv. of **7** and methyl iodide.

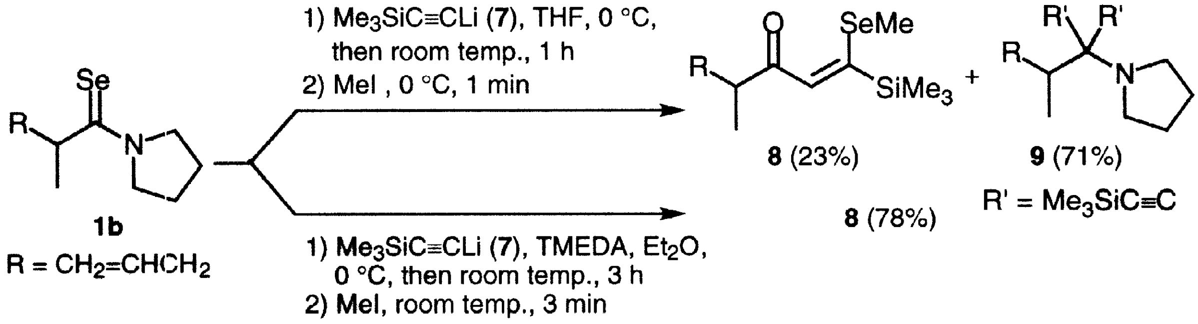
To detect some of the intermediates in the reaction with **7**, selenoamide **1i** was also reacted with 1 equiv. of **7** and methyl iodide in the presence of TMEDA in Et_2O. The ^{1}H and ^{13}C NMR spectra of the crude product showed that an allenyl selenide **12**[15] was formed. Thus, reactions with alkynyllithium **7** may proceed similarly to reactions with alkyllithiums to form **10**. Subsequent methylation at the selenium atom of **10** may give **11**, which instantly undergoes isomerization involving a 1,3-shift of a methylseleno group to form **12** as an intermediate.

Table 1 Conversion of selenoamides **1** with alkyllithiums to unsymmetrical ketones **2**[a]

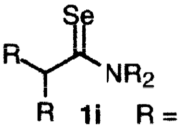


Entry	Selenoamide **1**[b] R	R'Li	Ketone **2**[b] Yield (%)[c]	Entry	Selenoamide **1**[b] R	R'Li	Ketone **2**[b] Yield (%)[c]
1	 **1c** (97 : 3)	CH_3Li[d]	**2c**[e] (96 : 4) 81%	2	 **1d** (97 : 3)	CH_3Li[d]	**2d**[e] (96 : 4) 78%
3	 **1e** (87 : 13)	n-C_4H_9Li	**2e**[f] (81 : 19) 64%	4	 **1f** (83 : 17)	n-C_4H_9Li	**2f** (67 : 33) 82%
5	 **1g**	CH_3Li	**2g** 56%(88%)[g]	6	 **1h** (Ar = 4-MeC_6H_4) (62 : 38)	CH_3Li[h]	**2h** (64 : 36) 65%

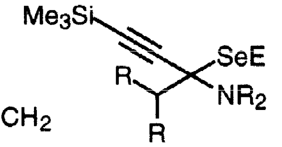
[a] Reactions of selenoamides **1** with alkyllithiums were carried out with THF as a solvent at 0 °C for 30 min as follows unless otherwise noted: selenoamides **1** (1 mmol), alkyllithiums (2 mmol), THF (5 mL). [b] The ratio of diastereomers is in parentheses. [c] Isolated yield. [d] 3 equiv. of methyllithium was used. [e] The relative stereochemistry of the isomers was tentatively determined by ^1H and ^{13}C NMR and PNOESY spectroscopy. [f] The stereochemistry was determined by the comparison of ^1H NMR spectra with those of similar γ,δ-unsaturated carbonyl compounds. [g] Crude yield is in parentheses. The crude product was obtained with purity higher than 95%, and purified through HPLC. [h] 2.2 equiv. of methyllithium was used.



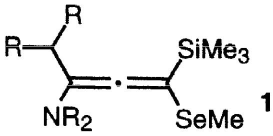
Scheme 3



1i R = $CH_2CH=CH_2$



10: E = Li
11: E = Me



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Further studies on these reactions of selenoamides and their mechanistic details are in progress.

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References and Notes

(1) For recent examples, see: (a) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, U.K., 1986. (b) *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Ed.; John Wiley & Sons: New York, 1986 and 1987; Vol. 1 and 2. (c) *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley-Interscience: New York, 1987.

(2) Krief, A. In *Comprehensive Organometallic Chemistry*; Abel, W. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, U.K., 1995; Vol. 11, p 515.

(3) (a) Ishihara, H.; Yoshimi, M.; Hara, N.; Ando, H.; Kato, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 835. (b) Kato, S.; Komuro, T.; Kanda, T.; Ishihara, H.; Murai, T. *J. Am. Chem. Soc.* **1993**, *115*, 3000. (c) Murai, T.; Ezaka, T.; Kanda, T.; Kato, S. *J. Chem. Soc., Chem. Commun.* **1996**, 1809. (d) Murai, T.; Ezaka, T.; Niwa, N.; Kanda, T.; Kato, S. *Synlett* **1996**, 865. (e) Murai, T.; Ezaka, T.; Ichimiya, T.; Kato, S. *Synlett* **1997**, 775.

(4) In a similar reaction of thioamides, thioketones were detected as an intermediate.[5] On the contrary, the generation of selenoketones, which have been the subject of great interest in recent years,[6] was not confirmed in the present reaction.

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(7) The reaction of an α-monosubstituted selenoamide with phenyllithium has been reported to give an enamine in a low yield, see: Sekiguchi, M.; Ogawa, A.; Fujiwara, S.; Ryu, I.; Kambe, N.; Sonoda, N. *Chem. Lett.* **1990**, 2053.

(8) Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517.

(9) For examples, see: (a) Wakefield, B. J. In *Organolithium Methods*; Academic Press: London, 1988; p 82. (b) O'Neill, B. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 1, p 397. (c) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (d) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15. (e) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

(10) The selenoamides **1c–h** were prepared by the allylation or aldol condensation of α-monosubstituted selenoamide.

(11) Typical experimental procedure for the synthesis of unsymmetrical ketones is as follows: To a solution of THF (5 mL) and selenoamides **1** (1 mmol) was added alkyllithiums (2 mmol) at 0 °C. The mixture was then stirred for 30 min at this temp., poured into brine and extracted with Et_2O three times. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was chromatographed through silica gel column with hexane–Et_2O as eluent to give the corresponding unsymmetrical ketones **2**.

(12) All new compounds gave satisfactory spectral and microanalytical data.

(13) Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739.

(14) The regio- and stereo-chemistry of the product **8** were determined by HMBC and PNOEZY spectroscopy.

(15) Braverman, S.; Duar, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5830.