Synthesis of α,β-Unsaturated Selenoamides by the Condensation Reaction of Lithium Eneselenolate Generated from Selenoacetamide with Aldehydes

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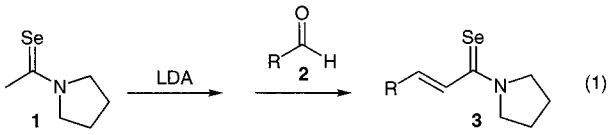
Received 14 April 1997

Abstract: The reaction of lithium eneselenolate generated from selenoacetamide and LDA with aldehydes gave α,β-unsaturated selenoamides in good to high yields. The successive addition of *n*-butyllithium and 3-bromo-1-propene to α,β-unsaturated selenoamide **3a** gave selenoamide **7** with high selectivity.

α,β-Unsaturated carbonyl[1] and thiocarbonyl[2] compounds are of great importance in organic syntheses. In contrast, much less attention has been paid to the chemistry of α,β-unsaturated selenocarbonyl compounds partly due to their instability and the lack of the suitable synthetic routes, although the synthesis of selenocarbonyl compounds has recently been a great topic in the chemistry of organoselenium compounds.[3] For example, α,β-unsaturated selenoaldehydes and ketones were generated but instantly underwent dimerization.[4] As isolable α,β-unsaturated selenocarbonyl compounds, β-phenyl[5,6] or β-alkenyl[7] α,β-unsaturated selenoamides have been reported. Unfortunately, the reported routes to α,β-unsaturated selenoamides have involved the use of metal complexes of selenoaldehydes[5] or disilyl selenide,[6] the preparation of which is fairly cumbersome. Furthermore, no alkyl substituted α,β-unsaturated selenoamides have been known to the best of our knowledge. We report herein the facile method for the synthesis of α,β-unsaturated selenoamides by the reaction of lithium eneselenolate generated from selenoacetamide and LDA with aldehydes.

The selenoacetamide **1**[8] was treated with LDA, which was generated from *n*-butyllithium and diisopropylamine, at 0 °C for 15 min. Then, to the reaction mixture was added 4-methylbenzaldehyde **2a** at 0 °C, and stirred at room temperature for 3 h (eq 1 and entry 1 in Table).[9] The aqueous work-up of the reaction mixture and purification with column chromatography gave α,β-unsaturated selenoamide **3a** as a deep red solid in 75% yield.

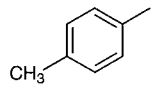
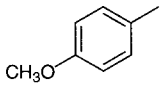
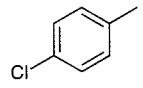
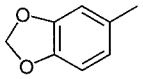


(1)

The results of the reaction using a variety of aldehydes are summarized in the Table.[10] The reaction with 4-methoxybenzaldehyde **2b** and piperonal **2d** proceeded smoothly to give the corresponding α,β-unsaturated selenoamides **3b** and **3d** in 71 and 72% yields, respectively (entries 2 and 4). On the other hand, the reaction with 4-chlorobenzaldehyde **2c** gave α,β-unsaturated selenoamide **3c** in only 29% yield although the starting selenoamide **1** was completely consumed (entry 3). Similarly to the reaction of aromatic aldehydes, the reaction with alkenyl and aliphatic aldehydes gave α,β-unsaturated selenoamides **3e–3g** in good yields (entries 5–7). ^{77}Se NMR spectra of α,β-unsaturated selenoamides **3a–3g** are also listed in Table. They were observed in the range of 531 ± 24.1 ppm, which were upfield in those of aliphatic and aromatic selenoamides.[11,12]

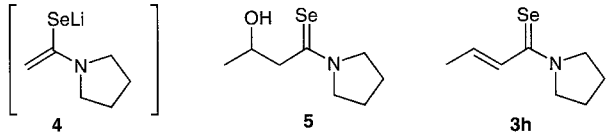
In the present reaction lithium eneselenolate **4**[13] is generated from **1** in the initial step analogous to the reaction of ordinary amides[14] and thioamides[15] with LDA. However, the low reactivity of **4** toward aldehydes is in sharp contrast to that of lithium enolate derived from

Table. Synthesis of α,β-Unsaturated Selenoamides **3**[a]

Entry	R	Aldehyde **2**	**3**	Yield[b] (%)	^{77}Se NMR[c] (ppm)
1		**2a**	**3a**	75%	507.4
2		**2b**	**3b**	71%	506.9
3		**2c**	**3c**	29%	555.1
4		**2d**	**3d**	72%	516.7
5		**2e**	**3e**	70%[d]	515.9
6	$(CH_3)_2CH$	**2f**	**3f**	71%	513.6
7		**2g**	**3g**	73%	511.9

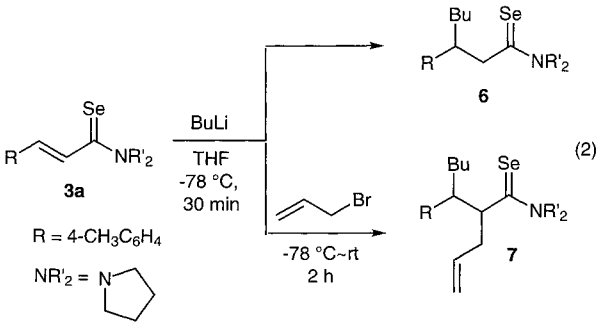
[a] The reaction was carried out with selenoamide **1** (1 mmol), LDA (1.2 mmol), and aldehyde (1 mmol) in THF (10 mL) at 20 °C for 3 h. [b] Isolated yield. [c] In $CDCl_3$. [d] Yield involves 5% of *Z,E*-isomer.

N,N-dimethylacetamide toward aldehydes. It has been reported that the aldol type reaction of *N,N*-dimethylacetamide with aldehydes proceeded even at -78 °C to give β-hydroxy amides quantitatively.[14] Furthermore, no β-hydroxy selenoamides were observed for the reaction of **1** except for the case of acetaldehyde, where α,β-unsaturated selenoamide **3h** was obtained in only 17% yield along with a 75% yield of β-hydroxy selenoamide **5**. The attempt to improve the yield of **3h** by the acidic aqueous work-up failed and gave only a 45% yield of **5** along with the starting selenoacetamide **1**.



Finally, the reactivity of α,β-unsaturated selenoamide **3a** was also tested. Alkylation of **3a** with *n*-butyllithium exclusively took place at the β-position of selenocarbonyl group at -78°C to give selenoamide **6** in 77% yield similarly to the reaction of α,β-unsaturated thioamides.[16] The addition of 3-bromo-1-propene to the reaction mixture prior to the aqueous work-up enabled the tandem alkylation-allylation to give selenoamide **7** in 70% yield as a single stereoisomer, although the

stereochemistry of **7** has not yet been determined. These results have proved the potential utilities of α,β-unsaturated selenoamides as new synthetic intermediates. Further progress will be reported in due course.



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

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(9) A typical experimental procedure is as follows: To a solution of LDA (1.2 mmol) and THF (10 mL) was added selenoacetamide **1** (0.176 g, 1 mmol) at 0 °C, and stirred for 15 min. Then, to this was added 4-methylbenzaldehyde (0.118 mL, 1.0 mmol) at 0 °C, and stirred at room temperature for 3 h. The mixture was poured into saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 three times. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was chromatographed through silica gel column with hexane-CH_2Cl_2 as eluent to give α,β-unsaturated selenoamide **3a** (75%).

(10) Selected spectroscopic data: **3a**: ^{1}H NMR ($CDCl_3$) δ 2.04 (m, 2H, NCH_2CH_2), 2.17 (m, 2H, NCH_2CH_2), 2.35 (s, 3H, Me), 3.68 (t, *J* = 14.0 Hz, 2H, NCH_2), 4.02 (t, *J* = 14.0 Hz, 2H, NCH_2), 6.92 (d, *J* = 15.0 Hz, 1H, C_6H_4CH=C*H*), 7.17 (d, *J* = 7.9 Hz, 2H, Ar), 7.47 (d, *J* = 7.9 Hz, 2H, Ar), 8.05 (d, *J* = 15.0 Hz, 1H, C_6H_4CH =CH); ^{13}C NMR ($CDCl_3$) δ 21.5, 24.0, 26.3, 51.8, 58.0, 126.7, 128.1, 129.6, 133.0, 140.2, 146.8, 193.1; Anal. Calcd for $C_{14}H_{17}NSe$: C, 60.43; H, 6.16. Found: C, 60.29; H, 6.17; **3b**: ^{1}H NMR ($CDCl_3$) δ 2.03 (m, 2H, NCH_2CH_2), 2.16 (m, 2H, NCH_2CH_2), 3.68 (t, *J* = 6.8 Hz, 2H, NCH_2), 3.83 (s, 3H, OCH_3), 4.02 (t, *J* = 7.1 Hz, 2H, NCH_2), 6.85 (d, *J* = 14.9 Hz, 1H, C_6H_4CH=C*H*), 6.88 (d, *J* = 8.7 Hz, 2H, Ar), 7.53 (d, *J* = 8.7 Hz, 2H, Ar) 8.07 (d, *J* =14.9 Hz, 1H, C_6H_4CH =CH); ^{13}C NMR ($CDCl_3$) δ 24.0, 26.2, 51.7, 55.3, 58.0, 114.3, 125.2, 128.4, 129.8, 146.8, 161.0, 192.7; Anal. Calcd for $C_{14}H_{17}NOSe$: C, 57.15; H, 5.82. Found: C, 56.87; H, 5.69; **3d**: ^{1}H NMR ($CDCl_3$) δ 2.03 (m, 2H, NCH_2CH_2), 2.16 (m, 2H, NCH_2CH_2), 3.67 (t, *J* = 6.8 Hz, 2H, NCH_2), 4.01 (t, *J* = 6.8 Hz, 2H, NCH_2), 6.00 (s, 2H, OCH_2O), 6.79 (d, *J* = 14.9 Hz, 1H, CHC=Se), 6.80 (d, *J* = 7.8 Hz, 1H, Ar), 7.08 (m, 2H, Ar), 8.01 (d, *J* = 14.9 Hz, C*H* =CHCSe); ^{13}C NMR ($CDCl_3$) δ 24.0, 26.2, 51.7, 57.9, 101.4, 106.3, 108.6, 124.6, 125.6, 130.1, 146.7, 148.2, 149.1, 192.0; Anal. Calcd for $C_{14}H_{15}NO_2Se$: C, 54.55; H, 4.90. Found: C, 54.37; H, 4.87; **3e** (*E,E*-isomer): ^{1}H NMR ($CDCl_3$) δ 1.81 (d, *J* = 4.9 Hz, 3H, Me), 2.01 (m, 2H, NCH_2CH_2), 2.14 (m, 2H, NCH_2CH_2), 3.58 (t, *J* = 13.9 Hz, 2H, NCH_2), 3.98 (d, *J* = 13.9 Hz, NCH_2), 6.24-6.27 (m, 2H, MeC*H*=C*H*-CH), 6.31 (d, *J* = 14.2 Hz, 1H, C*H*C=Se), 7.66-7.72 (m, 1H, CH-C*H*=CH); ^{13}C NMR ($CDCl_3$) δ 18.9, 23.9, 26.2, 51.6, 57.7, 128.5, 130.1, 139.2, 147.6, 192.7; Anal. Calcd for $C_{10}H_{15}NSe$: C, 52.63; H, 6.63. Found: C, 52.43; H, 6.57; **3f**: ^{1}H NMR ($CDCl_3$) δ 1.03 (d, *J* = 6.8 Hz, 6H, CH_3), 1.95 (m, 2H, NCH_2CH_2), 2.06 (m, 2H, NCH_2CH_2), 2.41 (m, 1H, Me_2CH), 3.51 (t, *J* = 13.9 Hz, 2H, NCH_2), 3.90 (t, *J* = 13.9 Hz, 2H, NCH_2), 6.28 (d, *J* = 14.6 Hz, 1H, CHC=Se), 7.18 (dd, *J* = 6.8, 14.6 Hz, 1H, CHC*H*=CH); ^{13}C NMR ($CDCl_3$) δ 21.5, 24.1, 26.3, 31.8, 51.7, 57.8, 128.3, 156.8, 194.3; Anal. Calcd for $C_{10}H_{17}NSe$: C, 52.17; H, 7.44. Found: C, 52.24; H, 7.41; **3g**: ^{1}H NMR ($CDCl_3$) δ 1.22 (m, 6H, cyclohexyl), 1.67 (m, 1H, cyclohexyl), 1.78 (t, *J* = 13.3 Hz, 4H, cyclohexyl), 2.01 (m, 2H, NCH_2CH_2), 2.13 (m, 2H, NCH_2CH_2), 3.58 (t, *J* = 6.6 Hz, 2H, NCH_2), 4.00 (d, *J* = 6.6 Hz, 2H, NCH_2), 6.29 (d, *J* = 14.7 Hz, 1H, CH=C*H*C=Se), 7.23 (dd, *J* = 14.7, 7.1 Hz, 1H, $C_6H_{11}CH$); ^{13}C NMR ($CDCl_3$) δ 23.9, 25.7, 25.9, 26.2, 31.8, 41.4, 51.7, 57.7, 128.5, 155.7, 194.1; Anal. Calcd for $C_{13}H_{21}NSe$: C, 57.77; H, 7.83. Found: C, 57.58; H, 8.03.

(11) For example, the signal of selenoacetamide **1** in ^{77}Se NMR spectrum is at 611.6 ppm, see also ref. 12.

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