Highly efficient one-pot synthesis of α,α-disubstituted selenoamides and their first reduction to amines

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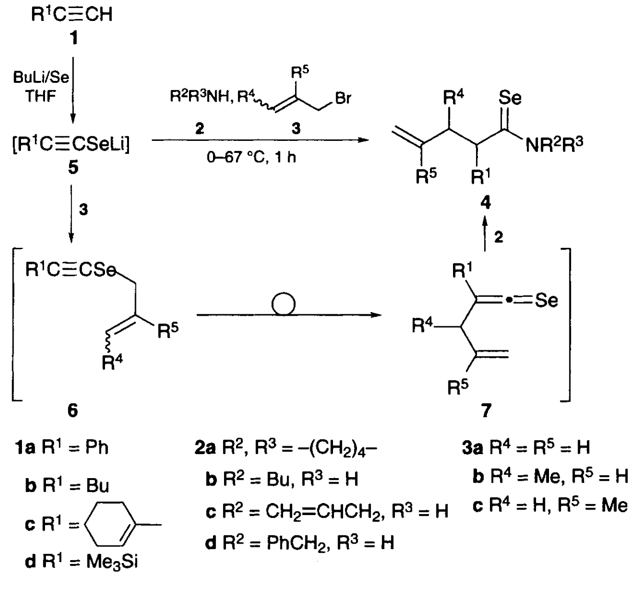
α,α-Disubstituted selenoamides are synthesized from terminal acetylenes, selenium, amines and allylic bromides in good to high yields; their reduction with $LiAlH_4$ affords alkenylamines quantitatively.

The synthesis, structure and reactivity of selenocarbonyl compounds have been extensively studied in recent years.[1] In contrast, the reactions of selenocarbonyl compounds for organic syntheses have been studied to lesser extent, which is partly due to the lack of general methods for their synthesis. Herein we report the highly efficient one-pot synthesis of α,α-disubstituted selenoamides from terminal acetylenes, selenium, amines and allylic bromides, and their first reduction to alkenylamines.

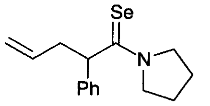
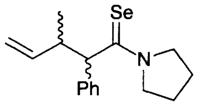
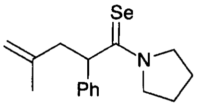
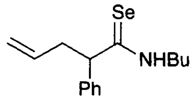
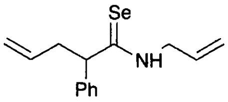
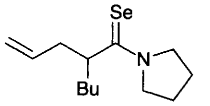
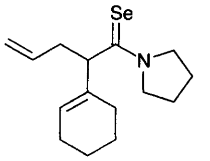
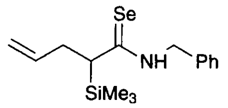
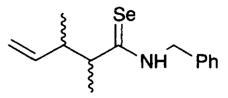
The reaction leading to α,α-disubstituted selenoamides is summarized in Scheme 1 and Table 1. For example, to a solution of THF and lithium alkyneselenolate **5** (R^1 = Ph) generated *in situ* from phenylacetylene **1a** were added pyrrolidine **2a** and allyl bromide **3a** successively at 0 °C. The resulting mixture was stirred at reflux temperature for 1 h. Subsequent column chromatography on silica gel gave the α,α-disubstituted selenoamide **4a** in 92% yield (entry 1). As shown in Scheme 1, the reaction may proceed through the initial formation of allylic alkynyl selenides **6** from lithium alkyneselenolates **5** and allylic bromides **3**.[2] Then, [3,3]-sigmatropic rearrangement of **6** may generate the selenoketene intermediates **7**, followed by the nucleophilic attack of amines **2** on **7** to form **4**.

Reaction with a variety of terminal acetylenes, amines and allylic bromides proceeded in a similar manner to afford the corresponding α,α-disubstituted selenoamides **4**.†,‡ In all cases, the successive addition of amines **2** and allylic bromides **3** is important in order to obtain the desired products **4** in good to high yields.§ Aryl, alkyl, alkenyl and silyl acetylenes were applicable to the present reaction (entries 1, 6, 7 and 8). α-Methylated selenoamide **4i** could be synthesized by using



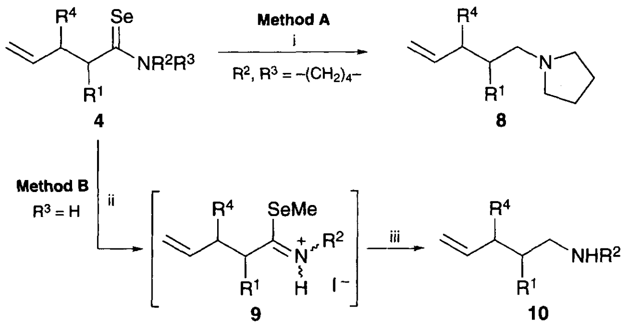
Scheme 1

Table 1 Synthesis of various α,α-disubstituted selenoamides[a]

Entry	Acetylene **1**, amine **2**, allylic bromide **3**	Product **4**	Yield (%)[b]
1	**1a, 2a, 3a**		**4a** 92
2	**1a, 2a, 3b**[c]		**4b**[d] 82
3	**1a, 2a, 3c**		**4c** 76
4	**1a, 2b, 3a**		**4d** 67
5	**1a, 2c, 3a**		**4e** 49
6	**1b, 2a, 3a**		**4f** 75
7	**1c, 2a, 3a**		**4g** 85
8[f]	**1d, 2d, 3a**		**4h** 59[g]
9[h]	MeCH=CHBr, **2d, 3b**[c]		**4i**[d] 66

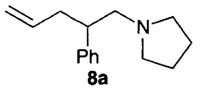
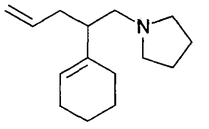
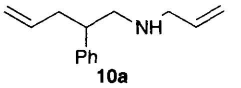
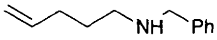
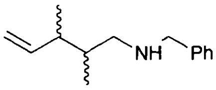
[a] The reaction was carried out with terminal acetylene (2 mmol), BuLi (2 mmol), Se (2 mmol), amine (2 mmol) and allylic bromide (2 mmol) in THF (5 ml) unless otherwise noted. [b] Isolated yield. [c] *E*:*Z* = 85:15. [d] The diastereoisomers were obtained in a range of about 50:50. [e] Stirred at 53 °C after the addition of 5 equiv. of allylanine. [f] 3 equiv. of benzylamine was used. The reaction mixture was washed with saturated aqueous $NaHCO_3$. [g] Yield including desilylated selenoamide (21%). [h] Propynyllithium was prepared by the reaction of 1-bromoprop-1-ene (2 mmol) with BuLi (4 mmol) in THF at −78 °C for 2 h. 5 equiv. of benzylamine was used.

propynyllithium prepared from 1-bromoprop-1-ene[3] (entry 9). Secondary selenoamides could be obtained from primary amines, although an excess of amine was necessary for the reactions of **2c,d** (entries 4, 5, 8 and 9). The allylated products at the nitrogen atom of primary amines[4] were not obtained. Crotyl bromide **3b** gave the corresponding products regioselectively, although with low diastereoselectivities (entries 2 and 9).



Scheme 2 *Reagents and conditions*: i, $LiAlH_4$, THF, 0 °C, 30 min, then room temp., 30 min–1 h; ii, MeI (5 equiv.), Et_2O, room temp., 24 h; iii, $LiAlH_4$, Et_2O, 0 °C, 10 min, then 35 °C, 3 h

Table 2 Reduction of α,α-disubstituted selenoamides

Entry	Selenoamide **4**	Method	Product **8, 10**	Yield (%)[a]
1[b]	**4a**	A	 **8a**	98
2[b]	**4g**	A	 **8b**	100
3[c]	**4e**	B	 **10a**	100
4[c]	**4h**	B	 **10b**	100
5[c]	**4i** (56:44)	B	 **10c** (56 : 44)	100

[a] The product was obtained with purity higher than 95% after the work-up of the reaction mixture. [b] The reaction was carried out with selenoamide (2 mmol) and $LiAlH_4$ (2 mmol) in THF. [c] The reaction was carried out with selenoamide (1 mmol), MeI (5 mmol) and $LiAlH_4$ (1 mmol) in Et_2O.

We next focused on the efficient conversion of the selenocarbonyl group to ordinary functional groups. After several disappointing results, reduction with $LiAlH_4$ successfully converted the selenocarbonyl group to a methylene group (Scheme 2).¶ The results of the reduction of α,α-disubstituted selenoamides **4** are summarized in Table 2. In most cases, the corresponding alkenylamines **8** and **10**, which are one of the most important but less accessible synthetic intermediates,[5] were obtained quantitatively, either by the direct reduction (Method A) or by the reduction *via* iminium salts **9** (Method B).|| Reduction of α-silylated selenoamide **4h** afforded the desilylated alkenylamine **10b** (entry 4).

Footnotes

† *Typical experimental procedure* for the synthesis of α,α-disubstituted selenoamides: To a solution of THF (5 ml) and lithium alkyneselenolate **5** prepared from terminal acetylene **1** (2 mmol), BuLi (1.6 M in hexane, 2 mmol, 1.25 ml) and Se powder (2 mmol, 0.158 g) were added amine **2** (2 mmol) and allylic bromide **3** (2 mmol) successively at 0 °C. The mixture was then stirred for 1 h at reflux, poured into saturated aqueous NH_4Cl 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–CH_2Cl_2 as eluent to give the corresponding α,α-disubstituted selenoamide **4**.

‡ All new compounds gave satisfactory spectral and microanalytical data.

§ Three selenoamides have been synthesized in a similar manner using dialkylamines but at most in 37% yield.[2]

¶ This result is in sharp contrast to the reduction of selenocarbonyl compounds such as seleno-ketones and -esters, in which the selenium atom remained in the final products.[6]

|| The similar reduction of some selenoamides with $NaBH_4$ in methanol gave a complex mixture.

References

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