Organoselenium-induced Cyclization of γ,δ-Alkenimines to Nitrogen Heterocycles

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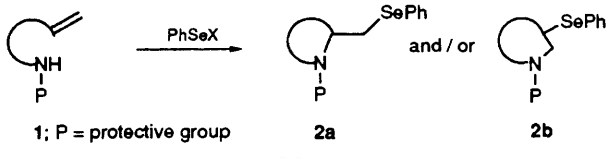
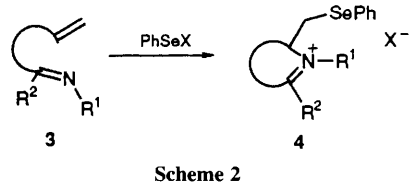
γ,δ-Alkenimines undergo electrophile-induced cyclization by means of phenylselenenyl bromide to produce cyclic iminium salts which are reduced to functionalized pyrrolidines or piperidines.

Phenylseleno-mediated synthesis of nitrogen heterocycles from alkenylamine derivatives is a known process with potential applications to alkaloid synthesis.[1] However, olefinic primary amines do not cyclize readily while *N*-protected olefinic primary amines do.[2] Electrophile-induced cyclizations with organoselenium reagents, *e.g.* phenylselenenyl halides or *N*-phenylselenophthalimide, have been reported with *N*-alkenylcarbamates,[2] *N*-alkenylamides,[3,4] *N*-alkenylimidates,[4,5] allylic ureas,[6] allylic isoureas[7] and *N*-alkenylsulfonamides.[8] Scheme 1 illustrates the conversion of these *N*-protected alkenylamines **1** with electrophilic selenium reagents into functionalized and *N*-protected nitrogen heterocycles, such as pyrrolidines and piperidines. The concomitant incorporation of the synthetically versatile seleno moiety has enabled further elaboration of these compounds as intermediates in a variety of syntheses of heterocycles.[9] The related iodofunctionaliza-



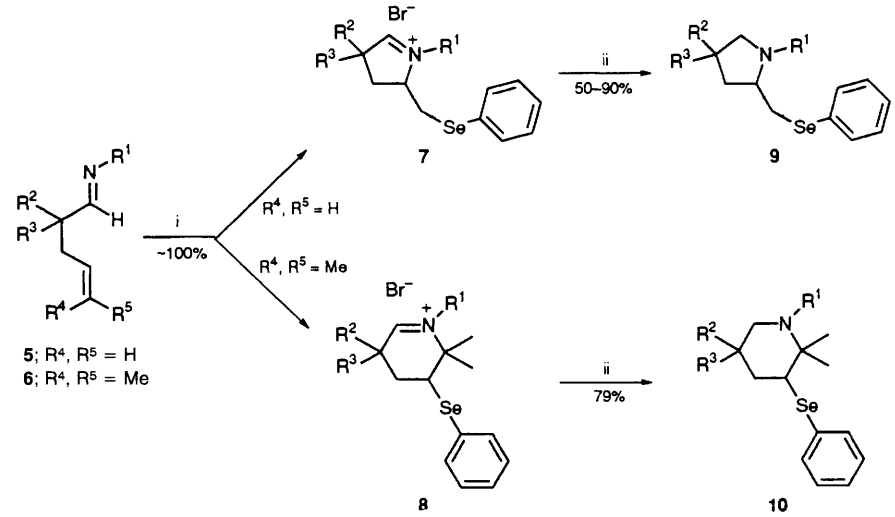
1; P = protective group **2a** **2b**

Scheme 1



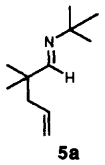
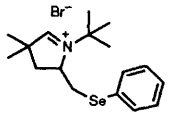
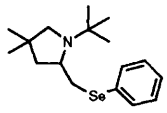
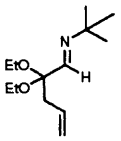
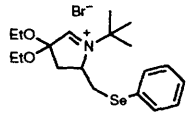
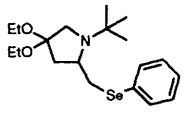
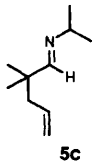
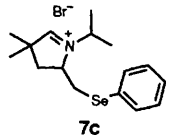
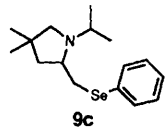
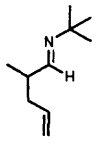
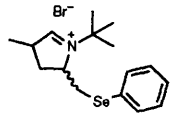
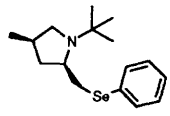
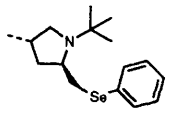
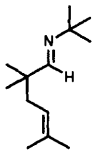
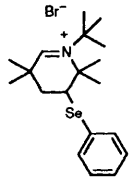
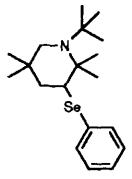
3 **4**

Scheme 2



Scheme 3 *Reagents and conditions*: i, PhSeBr, CH_2Cl_2, 0 °C, 10–30 min; ii, $NaBH_4$, MeOH–CH_2Cl_2, room temp., 1–2 h

Table 1 Conversion of γ,δ-alkenimines **5** and **6** into cyclic iminium compounds **7**, **8** and *N*-heterocycles **9**, **10**

Substrate	Cyclic iminium salt[a]	Yield (%)	*N*-Heterocycle[b]	Yield (%)[c]
 **5a**	 **7a**	100	 **9a**	90
 **5b**	 **7b**	100	 **9b**	50
 **5c**	 **7c**	100	 **9c**	84
 **5d**	 **7d**	–[d]	 *cis*-**9d**	32
			 *trans*-**9d**	32
 **6**	 **8**	100	 **10**	79

[a] *Reaction conditions*: reaction of γ,δ-alkenimines with phenylselenenyl bromide (1 equiv.) in dichloromethane at 0 °C for 10–30 min. [b] *Reaction conditions*: reaction of cyclic iminium salts with 1–2 equiv. of sodium borohydride in methanol at room temp. for 1–2 h. [c] Yield of isolated compounds, purified by flash chromatography (silica gel; EtOAc–Hexane). [d] The intermediate iminium salt was not isolated but directly reduced further to give a 1 : 1 mixture of *cis*- and *trans*-**9d**, which were separated by flash chromatography (silica gel; EtOAc).

tion of similar substrates **1** or the intramolecular aminomercuration of olefins offer an alternative synthetic methodology to nitrogen heterocycles.[1,10]

It is quite surprising that apart from imidates, no alkenimines have been used in such cyclization reactions. Such substrates **3** contain a weakly nucleophilic nitrogen atom which is able to displace the transient selenonium complex, formed upon addition of the electrophilic selenium species across the olefinic double bond, finally leading to cyclic iminium halides **4** (Scheme 2). Very recently, this strategy was performed with γ,δ- and δ,ε-alkenoximes (**3**; R^1 = OH) which gave phenylselenohalogenation of the olefinic double bond, the adduct being converted into the cyclic nitrone **4** (R^1 = OH) upon heating.[11] The latter communication urged us to disclose our own results on the selenium-induced electrophilic cyclization of alkenimines to cyclic iminium compounds and their further reactions into nitrogen heterocycles.

The reaction of γ,δ-alkenimines **5** (R^4, R^5 = H) with phenylselenenyl bromide in dichloromethane at 0 °C for 10–30 min gave rise to the formation of functionalized pyrrolin-1-ium bromides **7** in nearly quantitative yield (Table 1).† Also functionalized alkenimines, *e.g.* 2,2-diethoxypent-4-en-1-ylideneamine **5b**, cyclized smoothly to the corresponding iminium salts, which are suitable for further elaboration of the protected carbonyl moiety (Scheme 3). Analogously, selenium-induced cyclization of alkenimine **6**, carrying alkyl substituents at the olefinic unit, led to piperidin-1-ium bromide **8** in quantitative yield. The cyclic iminium compounds **7** and **8** are easily isolable by simple evaporation of the solvent. Reduction of these cyclic iminium salts with sodium borohydride in methanol–dichloromethane (1 : 1) afforded cleanly the corresponding functionalized pyrrolidines **9** and piperidine **10**.‡ It is not necessary to isolate or purify the cyclic iminium compounds as the crude products can be directly reduced further, as exemplified by the following experiments. Cyclization of *N*-(2-methylpent-4-en-1-ylidene)-*tert*-butylamine **5d** with phenylselenenyl bromide in dichloromethane gave rise to a stereoisomeric mixture of iminium bromides **7d**, which was reduced directly with sodium borohydride in methanol to afford a 1 : 1 mixture of *cis*- and *trans*-1-*tert*-butyl-4-methyl-3-phenylselenomethylpyrrolidine **9d**. Both stereoisomers were isolated in pure state by separation using flash chromatography.

In conclusion, a straightforward synthesis of functionalized pyrrolidines and piperidines from electrophilic selenium-induced cyclization of alkenimines has been developed. The easy access to the starting materials allow for a broad applicability. This strategy enables the direct synthesis of *N*-substituted pyrrolidines or piperidines, which has advan-

† Compounds **7** and **8** were fully characterized by spectroscopic methods. The spectral data of **7c** are given as an example: IR (NaCl, $CDCl_3$) ν/cm^{-1} 1661 (C=N). ^{1}H NMR ($CDCl_3$; 270 MHz): δ 1.45 and 1.56 (each 3H, each s, CMe_2); 1.46 and 1.63 (each 3H, each d, *J* 6.6 Hz, $CHMe_2$); 2.05 (1H, dd, J_{AB} 13.5, J_{AX} 7.6 Hz, $HCHCMe_2$); 2.45 (1H, dd, J_{AB} 13.5, J_{BX} 8.25 Hz, $HCHCMe_2$); 3.45 (1H, dd, J_{AB} 13.2, J_{AX} 7.6 Hz, CH–Se); 3.54 (1H, dd, J_{AB} 13.2, J_{BX} 3.6 Hz, CH–Se); 4.15 (1H, septet, *J* 6.6 Hz, $HCHMe_2$); 5.06–5.11 (1H, m, NCH); 7.30–7.35 (3H, *m*-, *o*- and *p*-CHs); 7.54–7.57 (2H, m, *m*-CHs); 9.81 (1H, br s, CH=N). ^{13}C NMR ($CDCl_3$; DEPT and HETCOR; 67.9 MHz): δ 21.01 and 21.65 ($CHMe_2$); 25.09 and 25.62 (CMe_2); 29.58 (CH_2Se); 40.36 (CH_2); 47.40 (CMe_2); 54.30 ($CHMe_2$); 70.33 (NCH); 127.76 (=C–Se); 128.07 (*p*-CH); 129.56 (*o*-CH); 133.28 (*M*-CH); 184.94 (C=N).

‡ Compounds **9a–d** and **10a** were fully characterized by spectroscopic methods. The spectral data of **9c** are given as an example: IR (NaCl) ν/cm^{-1} 1477, 1364, 738. ^{1}H NMR ($CDCl_3$; 270 MHz): δ 0.86 and 1.05 (each 3H, each d, *J* 6.48 Hz, $CHMe_2$); 0.99 and 1.12 (each 3H, each s, CMe_2); 1.57 (1H, dd, J_{AB} 13.0, J_{AX} 7.08 Hz, HCH–CMe_2); 1.76 (1H, dd, J_{AB} 13.0, J_{BX} 7.08 Hz, HCH–CMe_2); 2.34 and 2.65 (each 1H, each d, J_{AB} 8.92 Hz, NCH_2); 2.94–3.12 (4H, m, $Me_2CHNCHCH_2Se$); 7.18–7.26 (3H, *m*-, *o*-, and *p*-CHs); 7.45–7.50 (2H, m, *m*-CHs). ^{13}C NMR ($CDCl_3$, DEPT snf HETCOR; 67.9 MHz): δ 14.34 and 22.55 ($CHMe_2$); 28.82 and 29.63 (CMe_2); 33.55 (CH_2Se); 35.51 (CMe_2); 46.47 (CH_2); 48.00 (NCH); 59.41 ($NCHME_2$); 60.20 (NCH_2); 126.38 (*p*-CH); 128.88 (*o*-CHs); 131.27 (=C–Se); 132.20 (*m*-CHs). MS: *m/z* (%; only the peaks of the most abundant ^{80}Se isotope are reported) 311 (M^+; 1); 296(2); 155(8); 140(100); 138(4); 123(3); 112(5); 99(3); 98(40); 96(3); 95(3); 91(2); 83(2); 82(4); 81(5); 79(2); 78(2); 77(2); 71(2); 70(4); 69(3); 68(2); 67(2); 57(3); 56(9); 55(11); 44(5); 43(12); 42(9); 41(10).

tages over the known methodology given in Scheme 1. For this purpose, the latter method requires an additional deprotection–alkylation step, which is not necessary in the present cyclization procedure.

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