Organoselenium-induced Stereoselective Cyclisation of *O*-Allyl Oximes: A New Synthetic Route to Isoxazolidines

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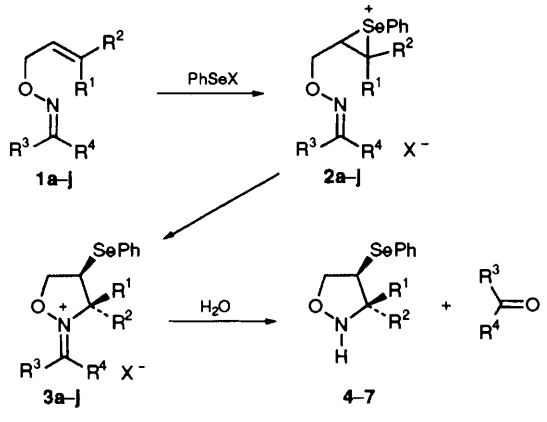
The organoselenium-induced ring-closure reactions of *O*-allyl oximes give cyclic iminium salts which react with water to afford isoxazolidines in good yield.

Electrophile-induced cyclisation of alkenes containing internal nitrogen nucleophiles is very useful in the synthesis of a variety of nitrogen heterocycles through the formation of a carbon–nitrogen bond.[1,2] Apart from the aminomercuriation,[3] primary alkenyl amines do not give the desired ring-closure reactions[4] unless *N*-protected.[4–7] Thus, several alkenyl amine derivatives like carbamates,[8–10] amides,[11,12] ureas,[13] imidates,[12,14,15] *O*-methyl isoureas[16] and hydroxamic acids[17–19] have been employed to effect cyclisation reactions with electrophilic reagents. Alkenyl imines cleanly undergo selenium- and bromine-induced electrophilic cyclisation to afford cyclic iminium compounds.[20,21] The ring-closure reaction of unsaturated oximes represents an interesting case which has recently attracted the attention of several research groups. The first examples were reported by Gallagher *et al.* and refer to the metal-induced cyclisations of allenic oximes which afford cyclic nitrones.[22] Grigg *et al.* have recently reported that cyclic nitrones can also be obtained from the mercuric acetate induced cyclisation of alkenyl oximes.[23] The selenium-induced cyclisation reactions of these compounds have also been investigated.[24,25] Terminal alkenyl oximes give rise to six-membered 1,2-oxazines and/or to five-membered cyclic nitrones. These latter are the major, and sometimes the sole, reaction products because, under theexperimental conditions employed, the starting oximes isomerize and the formation of the 1,2-oxazine is a reversible process.[25]

Here we disclose our results on a new selenium-induced cyclisation reaction, *i.e.* the conversion of the *O*-allyl oximes **1a–j** into the cyclic iminium salts **3a–j**, which represents a further example of the ease with which seleniranium ion intermediates, like **2a–j**, can be trapped by a weakly nucleophilic nitrogen atom. The cyclic iminium salts **3a–j** were not isolated,† but they were directly converted into the isoxazolidine derivatives **4–7** by simple treatment with water (Scheme 1).‡

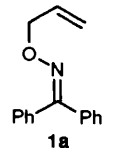
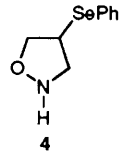
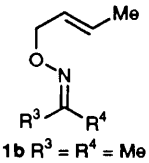
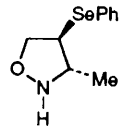
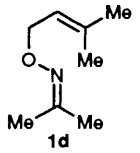
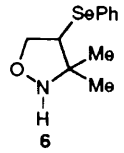
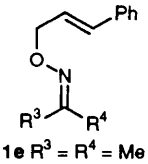
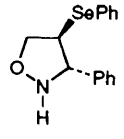
These experiments were carried out by adding, at room temperature, the *O*-allyl oximes **1a–j**§ to the solution of the phenylselenenylating agent[25] generated from diphenyl diselenide, ammonium persulfate and trifluoromethanesulfonic acid in acetonitrile. The solution rapidly turned from deep red to colourless. After 0.5 h the starting products were consumed (TLC) and the reaction mixtures were poured on water and worked up in the usual way. The reaction products were obtained in a pure form by column chromatography on silica gel and were identified¶ as the isoxazolidines **4–7**. Reaction yields are reported in Table 1. It is suggested that the cyclic iminium salts **3a–j** are formed as intermediates and that they easily suffer nucleophilic attack by water at the positive carbon atom to eventually afford the isoxazolidines **4–7** and the ketone or the aldehyde corresponding to the starting oxime (Scheme 1). Indeed, in most cases these were also isolated.‖



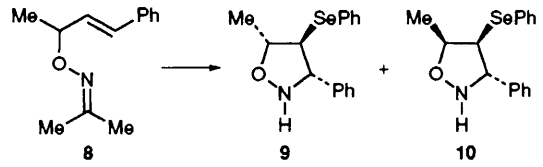
Scheme 1

Identical results were obtained from some experiments carried out under different experimental conditions. Thus, when phenylselenenyl bromide was employed to promote the cyclisation of **1b**, **d**, **e**, **f** and **h** and the reaction mixtures were then treated with water, the corresponding isoxazolidines could be isolated in good yield (Table 1). Moreover, with this phenylselenenylating agent it was also possible to unambiguously demonstrate that the cyclic iminium salts **3** are formed as intermediates. ^{1}H and ^{13}C NMR spectra of the salts **3b–f**, **3h** and **3i** could in fact be recorded when the reaction of the *O*-allyl

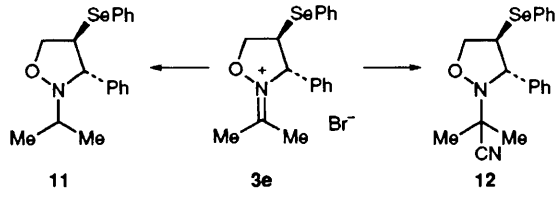
Table 1 Conversion of *O*-allyl oximes into isoxazolidines promoted by $(NH_4)_2S_2O_8$ and PhSeSePh[a]

O-Allyl oxime	Isoxazolidine	Yield (%)[b]
 **1a**	 **4**	90
 **1b** $R^3 = R^4 = Me$	 **5**	87 (95)
c $R^3 = R^4 = Pr^n$		81
 **1d**	 **6**	95 (95)
 **1e** $R^3 = R^4 = Me$	 **7**	74 (90)
f $R^3 = R^4 = Pr^n$		87 (87)
g $R^3 = R^4 = Ph$		60
h $R^3 = H$, $R^4 = Ph$		88 (83)
i $R^3 = H$, $R^4 = Me$		95
j $R^3 = Me$, $R^4 = Ph$		89

[a] The reactions were carried out according to the previously described general procedure.[25] [b] Yield in parentheses refers to the reactions carried out with PhSeBr.



Scheme 2



Scheme 3

oximes with PhSeBr was carried out in an NMR tube ($CDCl_3$).**

Compounds **5** and **7** were obtained as single stereoisomers indicating that, in agreement with other previously studied selenium-induced cyclisation reactions, the cyclic iminium salts **3a–j** and hence the isoxazolidines **4–7** are the result of a stereospecific *trans* addition process. In order to investigate the stereoselectivity of the cyclisation reaction, some experiments were carried out with the *O*-allyl oxime **8**. From the reaction carried out at room temperature a mixture (93%) of the two stereoisomers **9** and **10**, in a 8 : 2 ratio, was obtained (Scheme 2). The ratio changed to 7 : 3 and 6 : 4 by working at −20 and −40 °C, respectively. In this latter experiment the cyclisation reaction was promoted by PhSeCl/AgOTf.[27] The stereochemistry of **9** and **10** was assigned on the basis of the results of differential NOE experiments. Thus, irradiation of the Me resulted in a positive NOE on H_5 and H_4 in compound **9** and on H_5 and H_3 in compound **10**.

It can be anticipated that the cyclic iminium salts **3** can also react with other nucleophiles to afford products having different structures from the *N*-unsubstituted isoxazolidines observed from the reaction with water. Indeed, preliminary experiments showed that the bromide **3e** reacted with sodium borohydride and with sodium cyanide at room temperature, in the presence of methanol, to afford compounds **11** and **12** in 80 and 72% yield, respectively (Scheme 3). This production of isoxazolidines by a cyclisation reaction involving the formation of a carbon–nitrogen bond is very uncommon.[28]

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Footnotes

† Cyclic iminium salts were isolated by De Kimpe from the cyclisation of alkenyl imines promoted by phenylselenenyl bromide and by bromine.[20,21]

‡ While this manuscript was in preparation a report appeared describing the phenylselenenyl bromide induced cyclisation of γ- and δ-unsaturated oximes *O*-allyl ethers. In this case, however, the *O*-allyl group was not involved in the cyclisation reaction and the initially formed cyclic iminium salts suffered fragmentation at the oxygen–nitrogen bond leading to cyclic imines which were reduced to pyrrolidines and piperidines.[26]

§ Compounds **1a–j** were obtained from the corresponding oximes by treatment with NaH in THF and then with the desired allyl halide.

¶ Compounds **4–7** and **9–12** were fully characterized by spectroscopic methods. The spectral data of **5** are given as an example. ^1H NMR ($CDCl_3$; 200 MHz) δ 7.6–7.5 (m, 2H), 7.3–7.2 (m, 3H), 4.82 (s, br, 1H, H_2), 4.31 (dd, 1H, J = 7.8 and 8.8 Hz, H_5), 3.82 (dd, 1H, J = 5.9 and 8.8 Hz, $H_{5'}$), 3.49 (ddd, 1H, J = 4.9, 5.9 and 7.8 Hz, H_4), 3.38 (dq, 1H, J = 4.9 and 6.4 Hz,H_3), 1.19 (d, 3H, J = 6.4 Hz, Me); ^{13}C NMR ($CDCl_3$; 50.32 MHz) δ 134.5, 129.3, 128.3, 128.0, 76.1 (C_5), 62.8 (C_3), 49.1 (C_4), 17.2 (Me); GC-MS *m/z* (%; only the peaks of the most abundant ^{80}Se isotope are reported) 243 (2), 184 (100), 158 (27), 157 (22), 120 (15), 104 (19), 91 (17), 84 (17), 78 (33), 77 (28), 55 (52).

‖ Benzophenone, heptan-4-one, acetophenone and benzaldehyde were isolated from the reaction of **1a** and **1g**, **1c** and **1f**, **1j** and **1h**, respectively.

** *NMR data* of **3b** are given as an example: ^1H NMR ($CDCl_3$; 200 MHz) δ 7.4–7.2 (m, 5H), 5.18 (dq, 1H, J = 2.3 and 6.7 Hz), 5.1 (dd, 1H, J = 5.9 and 9.2 Hz), 4.72 (dd, 1H, J = 3.8 and 9.2 Hz), 4.05 (ddd, 1H, J = 2.3, 3.8 and 5.9 Hz), 2.5 (s, 3H), 2.3 (s, 3H), 1.65 (d, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$; 50.32 MHz) δ 166.3, 128.4, 127.4, 126.7, 77.1, 67.8, 41.6, 22.7, 21.0, 17.5.

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