1,4,2-Dioxazines or *N*-Acyl Isoxazolidines from Organoselenium-induced Cyclisation of *O*-Allyl Hydroxamic Acids

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O-Allyl hydroxamic acids easily give rise to organoselenium-induced cyclisation reactions to afford phenylseleno-substituted 1,4,2-dioxazines or *N*-acyl isoxazolidines as the kinetically or thermodynamically controlled products, respectively.

Recently the synthesis of nitrogen heterocyclic compounds by the electrophile-induced cyclisation of alkenes containing internal nitrogen nucleophile[1] has attracted great interest.

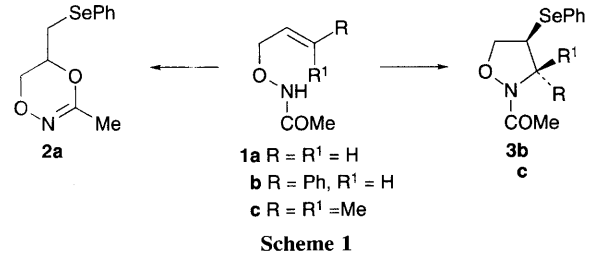
Recently we have reported that the selenium-induced cyclisation of γ-substituted β,γ-unsaturated hydroxamic acids can afford either five-membered cyclic *N*-hydroxy imidates or *N*-hydroxy γ-lactams under conditions in which product formation is either kinetically or thermodynamically controlled, respectively.[2]

We now report a new selenium-induced ring-closure reaction which can occur either through the oxygen or through the nitrogen atom of an ambident internal nucleophilic group as a function of the structure of the substrate and/or of the experimental conditions employed. Thus, *O*-allyl hydroxamic acids, **1**,† easily react with phenylselenenyl sulfate,[3] in acetonitrile, to afford the six-membered 1,4,2-dioxazines, **2**, or the five-membered *N*-acyl isoxazolidines, **3** (Scheme 1).‡,§ The oxygen atom of the carbonyl group or the nitrogen atom acts as the nucleophile in the formation of products **2** or **3**, respectively.

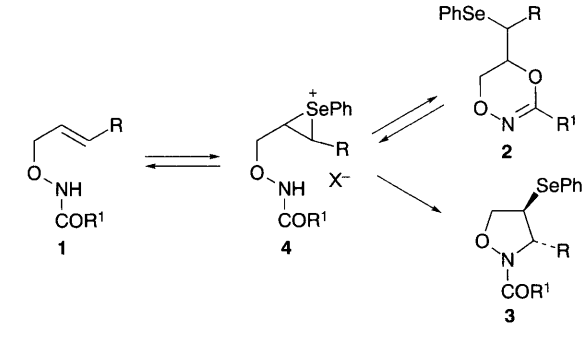
From the reactions carried out at room temperature the unsubstituted derivative **1a** gave the 1,4,2-dioxazine **2a** in 89% yield, whereas the substituted derivatives **1b** and **1c** afforded the *N*-acyl isoxazolidines **3b** and **3c** in 93 and 76% yield, respectively. Compound **3b** was obtained as a single stereoisomer indicating that the cyclization process is a stereospecific *trans* addition. The same reaction products were obtained from the reactions carried out either at −30 or 50 °C. Thus, in this case the nature of the reaction products is governed only by the structure of the starting *O*-allyl hydroxamic acid. In every case the cyclisation takes place with a Markovnikov orientation. The cyclisation of **1a** to the corresponding *N*-acyl isoxazolidine and those of **1b** and **1c** to the 1,4,2-dioxazines would require an *anti*-Markovnikov orientation.

The methyl derivative **1d** behaved differently (Scheme 2). At room temperature **1d** gave the *N*-acyl isoxazolidine **3d** (70%) and at −50 °C¶ gave the 1,4,2-dioxazine **2d** (82%). In the latter case, when the reaction mixture was left to reach room temperature before work up, the initially formed **2d** was converted into **3d**. Moreover, the *N*-acyl isoxazolidine **3d** was also obtained in 75% yield when the isolated 1,4,2-dioxazine **2d** was treated at room temperature with trifluoromethanesulfonic acid in acetonitrile. The formation of the 1,4,2-dioxazine is facilitated when the acetyl is substituted by a benzoyl group. Thus in the case of the *O*-allyl hydroxamic acid **1e**, the formation of the 1,4,2-dioxazine can be observed even at room temperature. A 1 : 5 mixture (93% yield) of **2e** and **3e** was in fact obtained from this experiment. Compound **2e** was the sole reaction product (68%) when the reaction was repeated at −30 °C. This could be easily converted into **3e** (78%) by treatment with acid at room temperature in acetonitrile. In these cases also the cyclisation reactions are stereospecific since **2d**, **2e**, **3d** and **3e** were all formed as single stereoisomers.

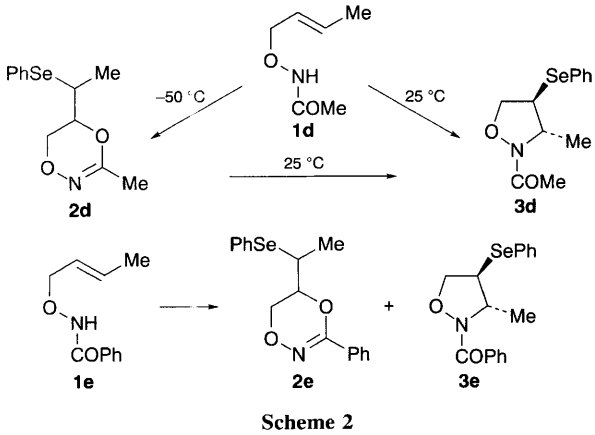
These results can be explained assuming that in the selenium-induced ring-closure reactions of the *O*-allyl hydroxamic acids



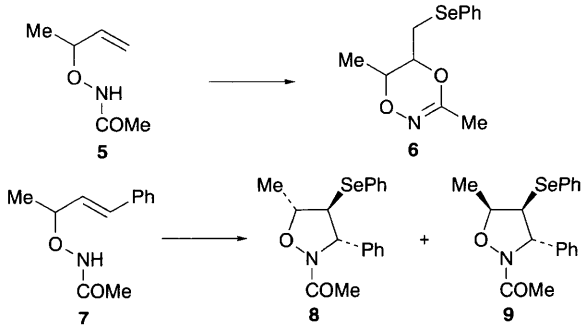
Scheme 1



Scheme 3



Scheme 2



Scheme 4

1d and **1e** product formation can be either kinetically or thermodynamically controlled. The trapping of the seleniranium intermediates **4** (Scheme 3) by the more nucleophilic oxygen atom, leading to the 1,4,2-dioxazines **2**, is faster than the trapping by the nitrogen atom, which leads to the *N*-acyl isoxazolidines **3**. However, under the experimental conditions employed, the formation of the 1,4,2-dioxazines is reversible. It is thus possible to direct the reaction towards one or the other of the two types of products using appropriate reaction conditions.

Finally, some experiments were carried out, at room temperature, with the substrates **5** and **7** (Scheme 4), from which it was expected to gain information concerning the selectivity of these cyclisation reactions. The reaction of **5** afforded a 1 : 1 mixture (determined by NMR) of the two stereoisomeric 1,4,2-dioxazines **6** (80%) which could not be separated. On the contrary, from the cyclisation of **7** the two stereoisomers **8** and **9** were obtained, in 81% yield, in a 8 : 1 ratio. The two products were separated and their stereochemistry was demonstrated by the results of differential NOE experiments and by conversion§ into the known[4] *N*-unsubstituted compounds.

Financial support from the CNR, Rome, Progetto Finalizzato 'Chimica Fine II', and Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Italy, is gratefully acknowledged.

Received, 26th September 1994; Com. 4/05842I

Footnotes

† Compounds **1a–e**, **5** and **7** were obtained from the corresponding hydroxamic acids by treatment with NaH in THF and then with the desired allyl halide or as reported in the literature.[5]

‡ The reactions were carried out according to the previously described procedure.[2,3] The *O*-allyl hydroxamic acids were added to the solution of the phenylselenenylating agent generated from diphenyl diselenide, ammonium persulfate and trifluoromethanesulfonic acid in acetonitrile. The solution rapidly turned from deep red to colourless. After 2 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.

§ Structures **2** and **3** were assigned on the basis of NMR and GC-MS spectra. The spectral data of **2d** and **3d** are given as an example. **2d**: ^{1}H NMR ($CDCl_3$; 200 MHz) δ 7.65–7.55 (m, 2 H), 7.35–7.29 (m, 3 H), 4.29 (dd, 1 H, J = 2.9 and 11.3 Hz), 4.21 (ddd, 1 H, J = 2.9, 6.8 and 8.4 Hz), 3.79 (dd, 1 H, J = 6.8 and 11.3 Hz), 3.29 (quint, 1 H, J = 7.9 Hz), 1.89 (s, 3 H), 1.51 (d, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$; 50.32 MHz) δ 155.4, 135.4, 129.2, 128.2, 127.6, 77.3, 66.0, 38.4, 17.7, 17.4. MS *m/z* (%; only the peaks of the most abundant ^{80}Se isotope are reported) 285 (M^+, 15), 243 (4), 184 (100), 182 (50), 157 (33), 120 (11), 77 (28), 55 (91), 43 (74). **3d**: ^{1}H NMR ($CDCl_3$; 200 MHz) δ 7.6–7.52 (m, 2 H), 7.38–7.23 (m, 3 H), 4.38–4.28 (m, 2 H), 3.74 (t, 1 H, J = 8.4 Hz), 3.52 (ddd, 1 H, J = 5.6, 6.5 and 8.4 Hz), 2.05 (s, 3 H), 1.3 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$; 50.32 MHz) δ 171.0, 135.2, 129.4, 128.5, 127.1, 74.6, 58.8, 47.1, 20.1, 19.6; GC-MS *m/z* (%) 285 (M^+, 13), 243 (4), 184 (97), 182 (47), 158 (20), 120 (9), 77 (15), 55 (53), 43 (100).

In several cases the structures of the *N*-acyl isoxazolidines **3** were also confirmed by conversion into the known *N*-unsubstituted compounds. These conversions were easily effected by treatment with DIBAL-H.

¶ This experiment was carried out with PhSeCl–AgOTf.[6]

References

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