N-Hydroxy γ-Lactams or Cyclic *N*-Hydroxy Imidates from the Organoselenium-induced Cyclization of β,γ-Unsaturated Hydroxamic Acids

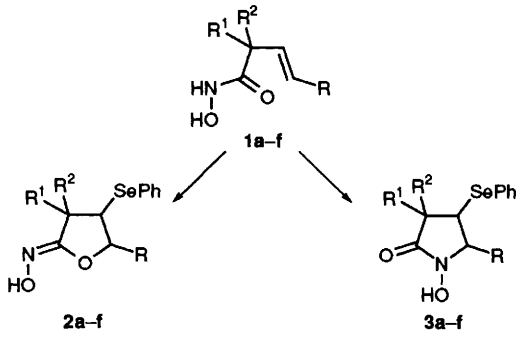
Marcello Tiecco,* Lorenzo Testaferri,* Marco Tingoli and Francesca Marini

Istituto di Chimica Organica, Facoltà di Farmacia, Università di Perugia, Italy

The organoselenium-induced ring-closure reactions of γ-substituted β,γ-unsaturated hydroxamic acids afforded cyclic phenylseleno *N*-hydroxy imidates or phenylseleno *N*-hydroxy γ-lactams as the kinetically or thermodynamically controlled products, respectively.

Phenylselenium-induced cyclization of alkenes containing internal nucleophiles is very useful in the synthesis of a variety of heterocyclic compounds.[1-3] Alkenols and alkenoic acids easily give cyclic ethers or lactones by addition of the electrophilic phenylselenium reagent to the double bond and subsequent cyclization by carbon–oxygen bond formation. Nitrogen heterocycles can be similarly prepared by the formation of a carbon–nitrogen bond, but primary alkenyl amines do not give the desired ring-closure reactions[4] unless *N*-protected.[3-7] Alkenimines, on the contrary, cleanly undergo selenium-induced electrophilic cyclization to give cyclic iminium compounds.[8] Interesting competitive reactions are observed when the nitrogen atom is incorporated in a functional group containing other nucleophilic atoms. It has recently been reported[9,10] that terminal alkenyl oximes give six-membered 1,2-oxazine and/or five-membered cyclic nitrones. In this case, however, there is no true competition since the formation of the carbon–oxygen or of the carbon–nitrogen bonds is dictated by the geometry of the starting oxime. The five-membered cyclic nitrones are the major, and sometimes the sole, reaction products because, under the experimental conditions employed, the starting oximes isomerize and the formation of the 1,2-oxazine is a reversible process.[10] The most interesting cases are those in which the two competing nucleophilic atoms can give rise to cyclization reactions giving cyclic compounds of the same size. This should be observed when alkenyl amides[11,12] or alkenyl ureas[13] are used. In both cases cyclization occurs exclusively through the formation of a carbon–oxygen bond. In order to induce the nitrogen atom to act as the nucleophilic site the structure of the starting products must be modified. Thus lactams or imidazolines are formed when the selenium-induced cyclization is effected starting from alkenyl imidates[12,14,15] or from the related alkenyl *O*-methyl isoureas,[16] respectively.

We now report that the selenium-induced cyclizations of γ-substituted β,γ-unsaturated hydroxamic acids **1a–f**† can give either the five-membered cyclic *N*-hydroxy imidates **2a–f** or the *N*-hydroxy γ-lactams **3a–f** (Scheme 1) depending on the experimental conditions used. This represents the first example of a ring closure reaction which can occur either through the oxygen or through the nitrogen atom of an ambident‡ internal nucleophilic group simply as a function of the reaction time and/or temp.



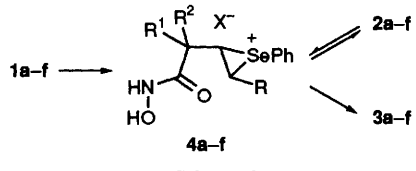
Scheme 1

β,γ-Unsaturated hydroxamic acids **1a–f** were added, at 25 °C, to the solution of the phenylselenenylating agent[10] generated, at room temp., from diphenyl diselenide, ammonium persulfate and trifluoromethanesulfonic acid in acetonitrile. The solution rapidly turned from deep red to colourless. The progress of the reaction was monitored by TLC and GC–MS. After 2 h the reaction mixture was worked up and the reaction products purified§ by column chromatography on silica gel. Rection yields are reported in Table 1. Under these experimental conditions, the γ-alkyl derivatives **1a–c** gave the cyclic *N*-hydroxy imidates **2a–c** (entries 1, 3 and 6)¶ whereas the γ-phenyl derivatives **1d–f** gave the *N*-hydroxy γ-lactams **3d–f** (entries 9, 11 and 13).‖

Starting from **1b**, it was observed that, if the reaction was left to proceed for longer (16 h), the initially formed imidate **2b** was converted into the γ-lactam **3b** (entry 4). Moreover, the γ-lactams **3a** and **3c** were obtained in good yields when the isolated imidates **2a** and **2c** were warmed at 50 °C for 2 h in acetonitrile in the presence of trifluoromethanesulfonic acid (entries 2 and 7, note *c*). Thus, when the reactions of the γ-alkyl derivatives **1a–c** were repeated, under the same conditions, but at 50 °C, the γ-lactams **3a–c** were directly obtained in good yield (entries 2, 5 and 7). In order to obtain the cyclic *N*-hydroxy imidates **2d–f** and to avoid the formation of the γ-lactams **3d–f**, the cyclization reactions of the γ-phenyl derivatives **1d–f** were carried out at −20 °C (entries 8, 10 and 12). These reactions were carefully monitored by TLC and were complete after 2 h. The cyclic imidate **2d** could not be isolated because it was converted into the corresponding lactone.[3]

Identical results were obtained under different experimental conditions. Thus the cyclization reactions of **1a** and **1d** promoted by PhSeCl–AgOTf,[19] in methylene chloride at room temp., gave **2a** and **3d** in 68 and 76% yield, respectively.

All these results can be explained assuming that in these selenium-induced ring-closure reactions of β,γ-unsaturated hydroxamic acids the product formation is either kinetically or thermodynamically controlled. The trapping of the seleniranium intermediates **4a–f** (Scheme 2) by the more nucleophilic oxygen atom, leading to the imidates **2a–f**, is faster than the trapping by the nitrogen atom, which leads to the γ-lactams **3a–f**. However, under the experimental conditions used, the formation of the imidates is reversible. It is thus possible to direct the reaction towards one or the other of the two products using appropriate reaction conditions. *N*-Hydroxy imidates or *N*-hydroxy γ-lactams can be obtained by kinetic control (room temp. for the alkyl and −20 °C for the phenyl derivatives) or by thermodynamic control (50 °C for the alkyl and room temp. for the phenyl derivatives), respectively. It is not unexpected that for the phenyl derivatives the reactions are faster than for the alkyl compounds.



Scheme 2

Table 1 Conversion of β,γ-unsaturated hydroxamic acids **1** into the cyclic *N*-hydroxy imidates **2** or into the *N*-hydroxy γ-lactams **3** promoted by ammonium persulfate and PhSeSePh[a]

Entry	Acid **1**	R	R^1	R^2	Temp. /°C	Time /h	Yield[b] of **2** (%)	Yield[b] of **3** (%)
1	**a**	Et	H	H	25	2	68	
2	**a**	Et	H	H	50	2		68[c]
3	**b**	Et	Me	Me	25	2	68	
4	**b**	Et	Me	Me	25	16		78
5	**b**	Et	Me	Me	50	2		75
6	**c**	Me	H	H	25	2	59	
7	**c**	Me	H	H	50	2		73[c]
8	**d**	Ph	H	H	−20	2	[d]	
9	**d**	Ph	H	H	25	2		87
10	**e**	Ph	H	Me	−20	2	51[e]	
11	**e**	Ph	H	Me	25	2		83[f]
12	**f**	Ph	Me	Me	−20	2	83	
13	**f**	Ph	Me	Me	25	2		71

[a] The reactions were carried out according to the previously described general procedure.[10] [b] Calculated from isolated products after column chromatography. [c] Compounds **3a** nd **3c** were obtained in 62 and 63% yield, respectively, from **2a** and **2c** in acetonitrile at 50 °C for 2 h in the presence of trifloromethanesulfonic acid. [d] Isolated as the corresponding lactone (78%). [e] Single stereoisomer, 25% of the corresponding lactone was also isolated. [f] 2:1 Mixture of two stereoisomers.

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, 7th September 1993; Com. 3/05358J

Footnotes

† Compounds **1a–f** were obtained from the corresponding carboxylic acids according to the general procedure reported in the literature.[17,18]

‡ Products deriving from the cylization through the oxygen atom of the OH group could not be detected. This process occurs easily with γ-unsubstituted β,γ-unsaturated hydroxamic acids.

§ Structures **2** and **3** were assigned on the basis of the chemical shifts of the protons in the 5 position and of the carbons 2 and 5. The spectra data of **2a** is given as an example. **2a**: IR ($CHCl_3$ solution) ν/cm^{-1} 3588 s, 3500–2800 br, 1691; ^{1}H NMR ($CDCl_3$; 200 MHz) δ 8.9 (br s, 1H, O*H*), 7.61–7.5 (m, 2H, *m*-C*H*), 7.38–7.2 (m, 3H, *o*- and *p*-C*H*), 4.29 (dt, 1H, *J* 4.5 and 7.3 Hz, OC*H*), 3.5–3.3 (m, 1H, SeC*H*), 3.02 (dd, 1H, *J* 7.8 and 16.6 Hz, *H*CHC=N), 2.67 (dd, 1H, *J* 8.9 and 16.6 Hz, HC*H*C=N). 1.91–1.52 (m, 2H, CH_2CH_3), 0.98 (t, 3H, *J* 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$; 50.32 MHz) δ 157.6 (C=N), 135.6, 129.2, 128.5, 126.3, 89.7 (OCH), 39.4 (SeCH), 34.2 (CH_2C=N), 25.9 [CH_2CH_3), 9.4 (CH_3); GC-MS *m/z* (%; only the peaks of the most abundant ^{80}Se isotope are reported) 285 (n^+, 17), 269 (4), 234 (6), 197 (10), 157 (72), 128 (100), 86 (67), 69 (72).

¶ Small amounts of the corresponding lactones were also present. The conversion of imidates into lactones is known to easily occur during the work up.[3]

‖ The related bromine-induced cyclization of γ-unsubstituted[17] or γ-alkyl[18] *O*-acyl β,γ-unsaturated hydroxamic acids is reported to give β-lactams, whereas the corresponding γ-phenyl derivative gives the γ-lactam.[18]

References

1 G. Cardillo and M. Orena, *Tetrahedron*, 1990, **46**, 3321.
2 K. C. Nicolaou, N. A. Petasis and D. A. Claremon, *Organoselenium-Based Ring Closure Reactions, in Organoselenium Chemistry*, ed. D. Liotta, J. Wiley, 1987, ch. 2, p. 127.
3 M. Tiecco, L. Testaferri, M. Tingoli, D. Bartoli and R. Balducci, *J. Org. Chem.*, 1990, **55**, 429.
4 D. L. J. Clive, V. Farina, A. Singh, C. K. Wong. W. A. Kiel and S. M. Menchen, *J. Org. Chem.*, 1980, **45**, 2120.
5 R. R. Webb II and S. Danishefsky, *Tetrahedron Lett.*, 1983, **24**, 1357.
6 A. Toshimitsu, K. Terao and S. Uemura, *J. Org. Chem.*, 1986, **51**, 1724.
7 M. A. Cooper and A. D. Ward, *Tetrahedron Lett.*, 1992, **33**, 5999.
8 N. De Kimpe and M. Boelens, *J. Chem. Soc., Chem. Commun.*, 1993, 916.
9 R. Grigg, M. Hadjisoteriou, P. Kennewell and J. Markandu, *J. Chem. Soc., Chem. Commun.*, 1992, 1537.
10 M. Tiecco, L. Testaferri, M. Tingoli, L. Bagnoli and F. Marini, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1989.
11 A. Toshimitsu, K. Terao and S. Uemura, *Tetrahedron Lett.*, 1984, **25**, 5917.
12 A. Toshimitsu, K. Terao and S. Uemura, *J. Chem. Soc., Chem. Commun.*, 1986, 530.
13 C. Betancor, E. I. León, T. Prange, J. A. Salazar and E. Suárez, *J. Chem. Soc., Chem. Commun.*, 1989, 450.
14 K. Terao, A. Toshimitsu and S. Uemura, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1837; A. Toshimitsu, K. Terao and S. Uemura, *J. Org. Chem.*, 1987, **52**, 2018.
15 For related iodofunctionalizations of imidates and thioimidates see: S. Knapp and A. T. Levorse, *J. Org. Chem.*, 1988, **53**, 4006; H. Takahata, T. Takamatsu and T. Yamazaki, *J. Org. Chem.*, 1989, **54**, 4812.
16 R. Freire, E. I. León, J. A. Salazar and E. Suárez, *J. Chem. Soc., Chem. Commun.*, 1989, 452.
17 G. Rajendra and M. J. Miller, *J. Org. Chem.*, 1987, **52**, 4471.
18 G. Rajendra and M. J. Miller, *Tetrahedron Lett.*, 1987, **28**, 6257.
19 S. Murata and T. Suzuki, *Chem. Lett.*, 1987, 849.