2-Oxazolines (4,5-Dihdro-oxazoles) by Organoselenium-induced Cyclisation of Allylic Ureas

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The reaction of allylic ureas with phenylselenenyl chloride in the presence of silica gel affords 2-oxazolines in good to excellent yields; 2-oxazolines are also stereospecifically obtained from β-phenylseleno ureas by chemoselective alkylation of the selenium atom followed by basic treatment.

The organoselenium-induced cyclisation of alkenic substrates leading to synthetically useful heterocyclic rings has been broadly investigated. Thus, cyclisation of alkenic alcohols,[1,2] thiols,[2] acids,[3] carbamates,[4] amides,[5] and imidates,[5,8] has been reported.

Previously, we reported a convenient synthesis of β-phenylseleno cyanamides[7] by acid-catalysed reaction of alkenes with *N*-phenylselenophthalimide and cyanamide, as well as a method for the preparation of β-phenylseleno carbamates.[8] This allows a great variety of allylic amine derivatives to be synthesised readily.

Here we report an efficient and stereoselective synthesis of 2-oxazolines by selenium-induced intramolecular functionalisation of allylic ureas (Scheme 1).

In a typical procedure, phenylselenenyl chloride (1.6 mmol) was added to urea (**1**) (1 mmol) in dry chloroform (120 ml) and silica gel (Merck, 0.063—0.2 mm, 4 g) under argon, and the suspension was stirred at 25 °C for 9 h. After usual workup and silica gel column chromatography 2-oxazoline (**2**) was obtained in 92% yield.†

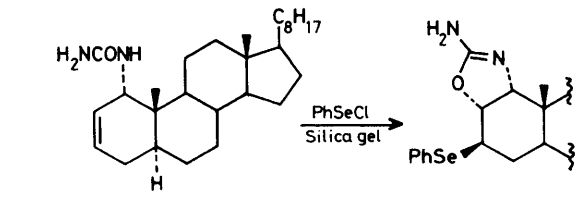
† New compounds gave satisfactory spectroscopic and analytical data. (**2**): i.r. ($CHCl_3$) 3450, 1670 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 4.52 (1H, dd, *J* 9.3, 6.5 Hz), 3.72 (1H, d, *J* 6.5 Hz), 3.12 (1H, m), 0.68 (3H, s), 0.62 (3H, s); ^{13}C n.m.r. ($CDCl_3$) δ 161.64 (C), 82.50 (CH), 70.58 (CH), 56.13 (CH); *m/z* 582, 584 (M^+).

As shown in Table 1, with the exception of substrate (**6**) (entry 3), cyclisation of allylic ureas proceeded through a 5-*exo* mode with the formation of a carbon–oxygen bond to afford 2-oxazolines. There is no clear explanation of the 6-*endo* cyclisation indicated in entry 3 that occurred by the nitrogen atom; however, there is a precedent in the cyclisation of a related alkenic amide.[9] Although the *exo* type process is the preferential pathway in selenium-induced cyclisations,[10] the exclusive formation of 2-oxazolines from the steroidal ureas (**1**) and (**8**) is noteworthy, since a six-membered heterocyclic ring produced by the opening of the episelenononium ion under conformational control (6-*endo* process) could be expected.

It is observed, that a diastereoisomeric *trans*/*cis* mixture with preferential *trans* stereoselection is obtained in the case

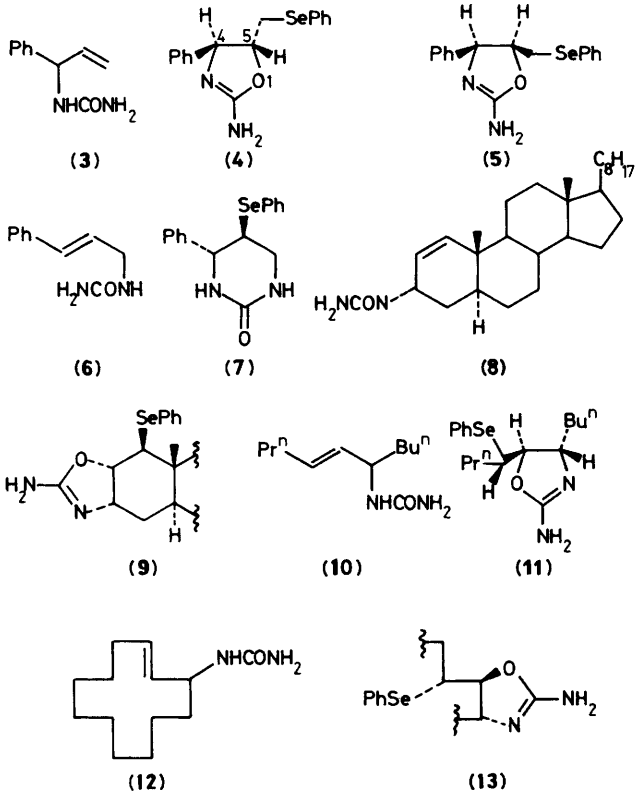
Table 1. Cyclisation of allylic ureas.

Entry	Urea	Temp./°C	Time/h	Product(s)	Yield/%
1	(**1**)	25	9	(**2**)	92
2	(**3**)	25	2	(**4**)	64
				(**5**)	32
3	(**6**)	25	19	(**7**)	42
4	(**8**)	25	6	(**9**)	76
5	(**10**)	40	4	(**11**)	81
6	(**12**)	30	7	(**13**)	91



(1) (2)

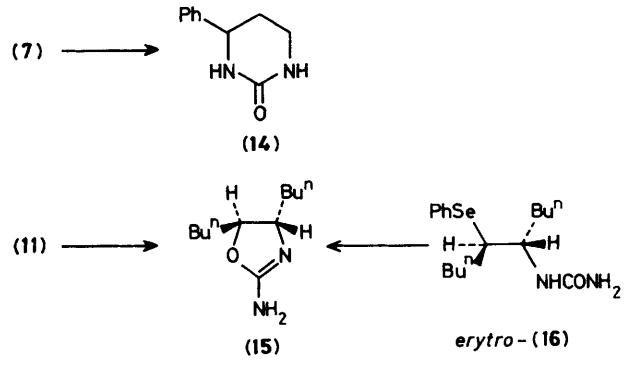
Scheme 1

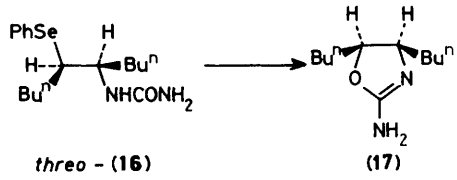


(3) (4) (5) (6) (7) (8)

(9) (10) (11)

(12) (13)





Scheme 2

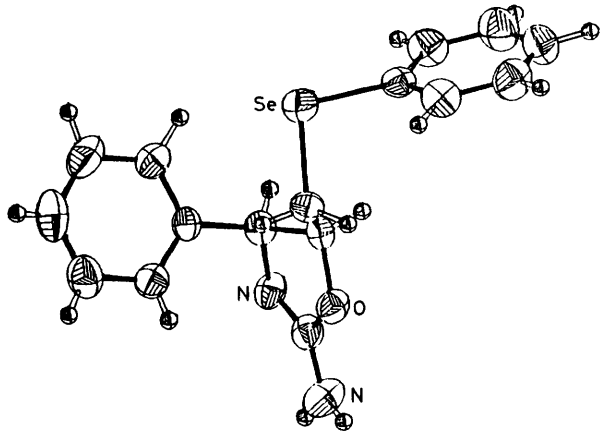


Figure 1. *X*-Ray crystal structure (ORTEP) of (**5**).

of the monosubstituted alkene (**3**) (entry 2). The assignment of *trans* and *cis* configuration to 2-oxazolines (**4**) and (**5**), respectively, is based on their ^{1}H n.m.r. spectra: (**4**), $J_{4H,5H}$ 5.4 Hz; (**5**), $J_{4H,5H}$ 8.6 Hz. The structure of (**5**) was unambiguously established by *X*-ray analysis (Figure 1).‡ On the other hand, 1,2-disubstituted alkenes give a single *E* stereoisomer as deduced from the small coupling constant observed between vicinal methine protons in the ^{1}H n.m.r. spectra of (**11**) and (**13**) (*J* 4.1 and 4.7 Hz, respectively). The configuration of the phenylseleno group is assigned presuming that an antiperiplanar opening of the episelenonium ion takes place.

If the silica gel is omitted in the reaction, the yield of 2-oxazoline decreases since uncyclised products arising by simple addition of phenylselenenyl chloride to the double bond are formed in variable amounts.

Reductive removal of the phenylseleno group of cyclic urea (**7**) and 2-oxazoline (**11**) was cleanly accomplished with triphenyltin hydride (2 equiv. toluene, 120 °C, 2 h) to afford (**14**) and (**15**) in 80 and 93% yield, respectively (Scheme 2).

2-Oxazolines are also stereospecifically obtained from β-phenylseleno ureas§ by chemoselective alkylation of the selenium atom and subsequent basic workup. Thus, alkylation of *erythro*-(**16**) with trimethyloxonium tetrafluoroborate (1.2 equiv., CH_2Cl_2, 25 °C, 24 h) followed by addition of di-isopropylethylamine (5 equiv. 25 °C, 2 h) gives the *E* 2-oxazoline (**15**) in 93% yield. The formation of the *Z* isomer (**17**) (83% yield) on identical treatment of *threo*-(**16**) supports the stereospecificity of this cyclisation.¶

‡ *Crystal data* for (**5**): $C_{16}H_{16}ON_2Se$, *M* = 330.0430, 332.0348, monoclinic, space group $P2_1/n$, a = 16.204, b = 16.845, c = 5.674 Å, β = 108.43°. The data were measured on a Philips PW-1100 four-circle automatic diffractometer operating with Cu-K_α radiation (λ = 1.5418 Å). The structure was solved by Patterson function analyses and refined with the SHELX-76 to R = 0.060. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ β-Phenylseleno ureas are quantitatively prepared by mild acid treatment of β-phenylseleno cyanamides[7] (0.075 M H_2SO_4, acetone/H_2O, 20/1, 25 °C, 20 h).

¶ *Selected spectroscopic and analytical data.* (**15**): ^{1}H n.m.r. ($CDCl_3$) δ 4.19 (1H, td, $J_{4H,5H}$ 5.7 Hz), 3.54 (1H, td); ^{13}C n.m.r. ($CDCl_3$) δ 35.83 (CH_2), 34.59 (CH_2); *m/z* 198 (M^+). (**17**): ^{1}H n.m.r. ($CDCl_3$) δ 4.65 (1H, td, $J_{4H,5H}$ 7.8 Hz), 3.92 (1H, td); ^{13}C n.m.r. ($CDCl_3$) δ 29.82 (CH_2), 28.56 (CH_2); *m/z* 198 (M^+).

It should be pointed out that the formation of heterocyclic rings through intramolecular nucleophilic displacement of the selenium group only has been reported previously, as far as we know, in the synthesis of epoxides from β-hydroxyselenides, and tetrahydrofurans from δ-hydroxyselenides.[11]

Selenium-free 2-oxazolines can be subsequently hydrolysed[12] to yield vicinal amino alcohols, a unit frequently observed in biologically active compounds such as aminocyclitol and amino-sugar antibiotics.

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