



## New Synthesis of Isoxazolidines from the Selenium-Induced Cyclization of O-Allyl Hydroxylamines

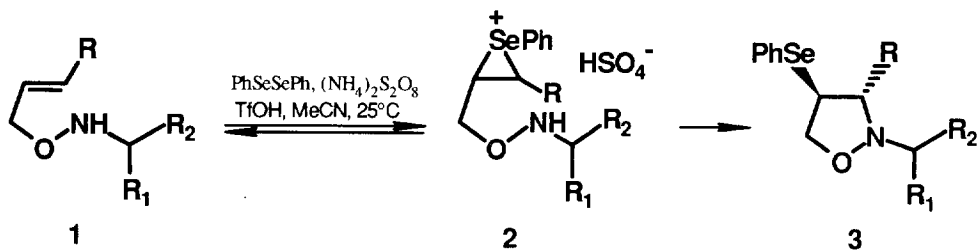
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**Abstract:** The reaction of O-allyl hydroxylamines with phenylselenenyl sulfate, generated from the oxidation of diphenyl diselenide with ammonium persulfate, easily affords N-alkyl isoxazolidines as the result of a cyclization reaction through the formation of a carbon-nitrogen bond.

The cyclization reaction of alkenes containing internal nitrogen nucleophiles, promoted by electrophilic reagents, represents a very useful method to easily obtain a wide range of substituted nitrogen heterocycles.<sup>1,2</sup> Thus, a variety of alkenylamine derivatives, such as carbamates,<sup>3</sup> amides,<sup>4</sup> imidates,<sup>5</sup> ureas,<sup>6</sup> isoureas,<sup>7</sup> hydroxamic acids,<sup>8</sup> oximes,<sup>9,10</sup> imines,<sup>11</sup> etc. have been employed to effect ring closure reactions by treatment with several electrophilic reagents. Competitive reactions are observed when the nitrogen atom is incorporated in a functional group containing other nucleophilic atoms, as in the cases of amides, ureas, hydroxamic acids and oximes. Thus, the success of these ring closure reactions is strongly influenced by the structure of the functional group containing the nitrogen atom as well as by the experimental conditions employed.

Scheme 1



We now report a new selenium-induced cyclization reaction in which the heterocyclic ring is generated by the formation of a carbon-nitrogen bond and which do not give rise to any other competitive

process. Thus, the reactions of the O-allyl hydroxylamines **1** with phenylselenenyl sulfate<sup>8,10</sup> afford the N-alkyl isoxazolidines **3** in good yield (Scheme 1). This represents a new and very convenient method to obtain this interesting class of heterocyclic compounds.<sup>12</sup>

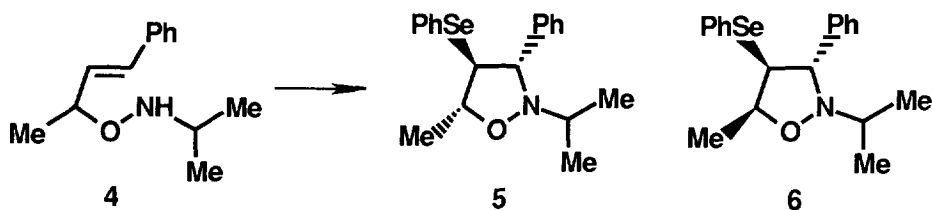
The O-allyl hydroxylamines **1a-f**, employed for the present investigation, are indicated in Table 1. These were conveniently obtained from the corresponding O-allyl oximes<sup>13</sup> which were reduced, at room temperature, with sodium cyanoborohydride and hydrochloric acid in methanol. Apart from **1b**, all the O-allyl hydroxylamines employed have a *trans* configuration.

The cyclization reactions were carried out by adding the O-allyl hydroxylamines **1a-f** 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. The progress of the reaction was monitored by TLC and GC-MS. After about 2 h the starting products were consumed and the reaction mixtures were poured in water and worked up in the usual way. The reaction products **3a-f** were obtained in a pure form by column chromatography on silica gel and were fully characterized by <sup>1</sup>H and <sup>13</sup>C NMR and GC-MS spectra. The results of these experiments are summarized in Table 1.<sup>14</sup>

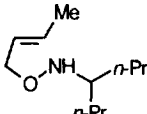
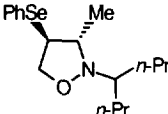
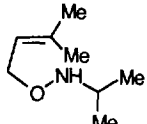
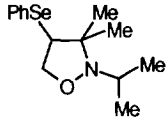
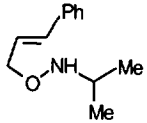
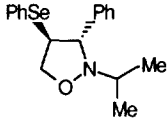
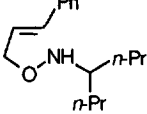
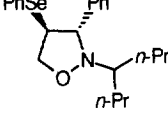
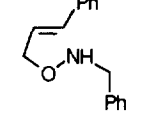
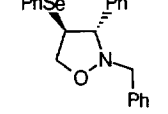
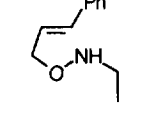
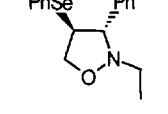
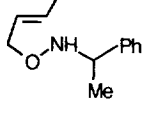
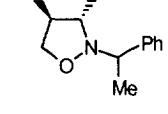
Compounds **3a** and **3c-3f** were obtained as single stereoisomers indicating that, in agreement with other previously studied selenium-induced cyclization reactions, the isoxazolidines **3** are the result of a stereospecific *trans* addition process which, as indicated in Scheme 1, involves the formation of the seleniranium ion intermediate **2**. Because of the structure of the alkyl group linked to the nitrogen atom, the O-allyl hydroxylamine **1g** gave rise to a 1:1 mixture of two stereoisomers **3g** (96% yield) which could be separated by column chromatography.

In order to investigate the stereoselectivity of the cyclization reaction, an experiment was carried out with the O-allyl hydroxylamine **4** (Scheme 2). The presence of a methyl substituent has no influence on the course of the reaction since the two possible stereoisomers **5** and **6** were obtained in equimolecular amounts (90% yield). The two compounds were separated and their stereochemistry was demonstrated by the results of differential NOE experiments. Thus, irradiation of the Me group at the 5-position resulted in a positive NOE on H<sub>5</sub> and H<sub>4</sub> in compound **5** and on H<sub>5</sub> and H<sub>3</sub> in compound **6**. Moreover, the stereochemistry of the two isomers was fully established by the results of NOESY experiments.

Scheme 2



**Table 1.** Conversion of O-Allyl Hydroxylamines into Isoxazolidines Promoted by PhSeSePh, (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> and CF<sub>3</sub>SO<sub>3</sub>H.

O-Allyl Hydroxylamine	Isoxazolidine	% Yield
<b>1a</b> 	<b>3a</b> 	73
<b>1b</b> 	<b>3b</b> 	79
<b>1c</b> 	<b>3c</b> 	67
<b>1d</b> 	<b>3d</b> 	85
<b>1e</b> 	<b>3e</b> 	85
<b>1f</b> 	<b>3f</b> 	56
<b>1g</b> 	<b>3g</b> 	96

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- O-Allyl oximes were obtained from the corresponding oximes by treatment with NaH in THF and then with the desired allyl halide. The hydroxylamines **1a-g** and **4**, obtained from the reduction of the O-allyl oximes, were fully characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR and GC-MS spectra.
- N-Alkyl isoxazolidines **3** can also be obtained from the phenylselenenyl bromide induced cyclization of O-allyl oximes followed by reduction of the corresponding cyclic iminium salts. Unpublished results from this laboratory.

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