Electrochemical selenium-initiated cyclization of alkenyl hydantoins

Biljana M. Šmit*a, Zoran Simića, Darko Ašanin*a, Radoslav Z. Pavlovićb

*aFacuilty of Science, University of Kragujevac, Radoja Domanovića 12 P.O. Box 60, 34000 Kragujevac, Serbia, biljam@kg.ac.rs
bFaculty of Chemistry, University of Belgrade, Studentski trg 12-16, 11158 Belgrade, Serbia

Abstract: 5-Alkenyl hydantoins are converted into bicyclic or tricyclic hydantoins under indirect electrochemical conditions generating selenium cations. Regiospecific 5-exo ring closure process occurred. The reactions proceeded in good yields and the influence of electrochemical conditions on diastereoselectivity of the reactions is investigated.

Key words: selenium, hydantoins, cyclization, electrosynthesis, selectivity

Introduction

The hydantoin moiety occurring in various biologically active compounds represents a pharmaceutical importance most notably known due to their antimicrobial, anticancer and anticonvulsant activity1. The observed activities do not arise from the hydantoin
nucleus itself but from different substituents that have been appended to it. In particular, spirohydantoins and fused polycyclic hydantoin derivatives have recently attracted much attention in drug discovery due to their various biological activities.

Selenocyclization proved to be a powerful and versatile tool for the construction of heterocyclic rings. Recently we described a new methodology for the synthesis of the bicyclic and tricyclic hydantoin scaffold and our independent efforts to exploit intramolecular selenocyclization for fashioning molecules having rigid, conformationally well-defined structures consistent with attractive lead compounds for drug discovery. In this work we decide to utilize electrochemically generated phenylselenyl cation in the cyclization of 5-alkenyl hydantoins and alkenyl spirohydantoins and explore whether this conditions have effect on the reaction, especially on regio- and stereoselectivity.

**Results and discussion**

The alkenyl hydantoins contain a double bond and an internal nitrogen nucleophile, and they could be suitable substrates for intramolecular electrophilic cyclization. Over several decades, electrophilic selenium reagents have been proven to be quite useful for this purpose. In some cases electrochemical selenylations have advantages over other related methods.

The cyclization of previously synthesized 5-alkenyl hydantoins 1a-g and alkenyl spirohydantoins 1h-j was performed by means of electrochemically generated phenylselenyl cation from diphenyldiselenide in a MeCN solution of NaClO₄. Perchlorate in this process serves as mediator. We tried to perform the reaction with other mediators (LiCl, KBr, KI) but NaClO₄ gave the best results. Easy oxidation of perchlorate at the anode provides *in situ* generation of PhSe⁺ cation capable of reacting with the π-electronic system of substrate. The reaction is chemo- and regiospecific giving only one regioisomer stemming from the nucleophilic attack of the nitrogen atom to cyclic seleniranium ion intermediate during the cyclization step. Formation of this sole regioisomer proceeds via favorable 5-exo-trig ring closure process and it is both
kinetically and thermodynamically favored. Separable diastereomeric bicyclic or tricyclic hydantoin derivatives, cis-2a-j and trans-2a-j were obtained in good to excellent yield. The products with bridgehead substituent and CH$_2$SePh group in cis relationship were formed predominantly. The observed diastereomeric ratios and chemical yields are summarized in Table 1.

Scheme 1. Selenocyclization of alkenyl 1a-g and alkenyl spirohydantoins 1h-j

In comparison with the previously obtained results$^{5,6}$ diastereoselectivity is lower. Cis diastereoisomer is still predominant but the amount of trans is much higher. Even in the case of 2h the diastereomeric ratio is inverse and trans isomer is predominant.

Further investigations are in progress. We will try to tune the reaction conditions and find out the way to direct cyclization in stereoselective manner to form thermodynamically favored trans diastereomer.
Table 1. Selenocyclization of alkenyl hydantoins 1a-g and alkenyl spirohydantoins 1h-j

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Products</th>
<th>Yield [%]</th>
<th>dr cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td><img src="image1" alt="Structure" /></td>
<td><img src="image2" alt="Structure" /></td>
<td>72</td>
<td>85:15</td>
</tr>
<tr>
<td>b</td>
<td><img src="image3" alt="Structure" /></td>
<td><img src="image4" alt="Structure" /></td>
<td>88</td>
<td>51:49</td>
</tr>
<tr>
<td>c</td>
<td><img src="image5" alt="Structure" /></td>
<td><img src="image6" alt="Structure" /></td>
<td>96</td>
<td>53:47</td>
</tr>
<tr>
<td>d</td>
<td><img src="image7" alt="Structure" /></td>
<td><img src="image8" alt="Structure" /></td>
<td>63</td>
<td>69:31</td>
</tr>
<tr>
<td>e</td>
<td><img src="image9" alt="Structure" /></td>
<td><img src="image10" alt="Structure" /></td>
<td>73</td>
<td>71:29</td>
</tr>
<tr>
<td>f</td>
<td><img src="image11" alt="Structure" /></td>
<td><img src="image12" alt="Structure" /></td>
<td>63</td>
<td>67:32</td>
</tr>
<tr>
<td>g</td>
<td><img src="image13" alt="Structure" /></td>
<td><img src="image14" alt="Structure" /></td>
<td>75</td>
<td>54:45</td>
</tr>
<tr>
<td>h</td>
<td><img src="image15" alt="Structure" /></td>
<td><img src="image16" alt="Structure" /></td>
<td>86</td>
<td>12:88</td>
</tr>
<tr>
<td>i</td>
<td><img src="image17" alt="Structure" /></td>
<td><img src="image18" alt="Structure" /></td>
<td>97</td>
<td>69:31</td>
</tr>
<tr>
<td>j</td>
<td><img src="image19" alt="Structure" /></td>
<td><img src="image20" alt="Structure" /></td>
<td>82</td>
<td>72:28</td>
</tr>
</tbody>
</table>
Experimental

General procedure for electrochemical selenocyclization of hydantoins (1a-j)

A solvent of 1a-j (1 mmol), Ph₂Se₂ (156 mg, 0.5 mmol), silica gel (150 mg, 5 mmol) and NaClO₄ (123.5 mg, 1 mmol) in MeCN (10 ml) was placed in an undivided electrolysis cell and electrolysed under a constant current (10 mA) at ambient temperature. After completion the reaction mixture was stirred overnight. The solvent was distilled off, residue dissolved in CH₂Cl₂, washed with sat. NaHCO₃ solution and brine, and dried over anh. Na₂SO₄. The solvent was evaporated and the reaction mixture was analyzed by TLC and ¹H NMR spectroscopy.

Acknowledgements

This work is part of the scientific activity of the multidisciplinary group “SeS Redox and Catalysis” at the Faculty of Science, University of Kragujevac, Serbia. Part of this work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Pr. No. 172016).

References


