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Electrochemical selenium-initiated cyclization of alkenyl hydantoins

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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 activity[1]. The observed activities do not arise from the hydantoin

nucleus itself but from different substituents that have been appended to it.[2] In particular, spirohydantoins[3] and fused[4] polycyclic hydantoin derivatives have recently attracted much attention in drug discovery due to their various biological activities.

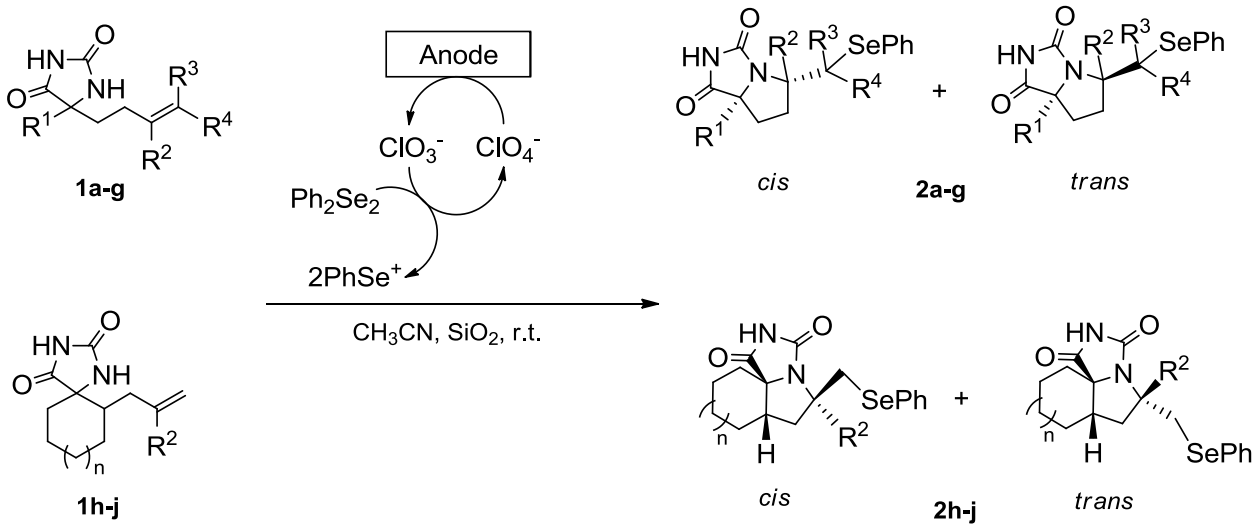
Selenocyclization proved to be a powerful and versatile tool for the construction of heterocyclic rings.[5] Recently we described a new methodology for the synthesis of the bicyclic and tricyclic hydantoin scaffold and our independent efforts to exploit intramolecular selenocyclization for fashioning molecules having rigid, conformationally well-defined structures consistent with attractive lead compounds for drug discovery.[6] 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.[7]

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 $NaClO_4$. Perchlorate in this process serves as mediator. We tried to perform the reaction with other mediators (LiCl, KBr, KI) but $NaClO_4$ 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.[8] 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_2SePh group in *cis* relationship were formed predominantly. The observed diastereomeric ratios and chemical yields are summarized in Table 1.



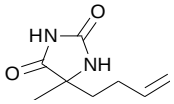
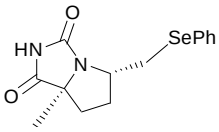
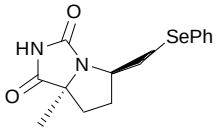
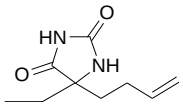
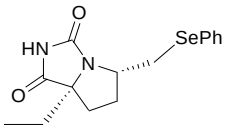
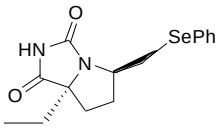
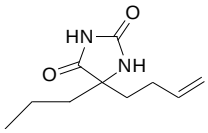
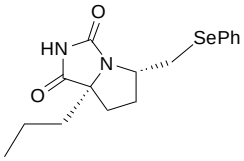
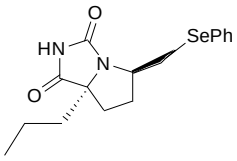
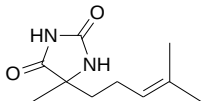
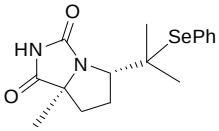
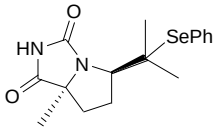
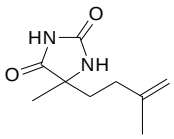
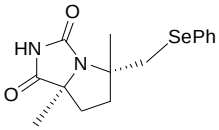
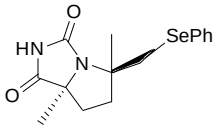
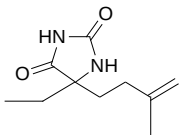
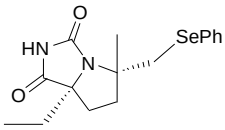
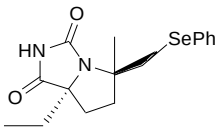
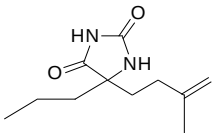
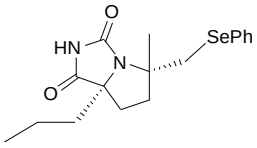
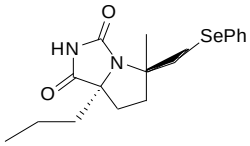
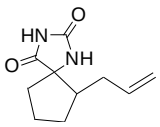
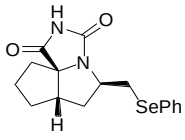
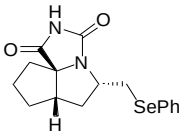
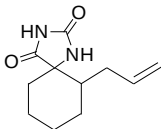
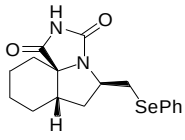
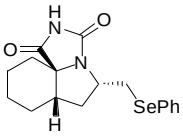
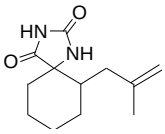
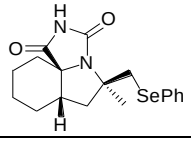
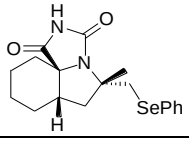
1a, 2a: R^1 = Me, R^2 = R^3 = R^4 = H
1b, 2b: R^1 = Et, R^2 = R^3 = R^4 = H
1c, 2c: R^1 = Pr, R^2 = R^3 = R^4 = H
1d, 2d: R^1 = R^3 = R^4 =Me, R^2 = H
1e, 2e: R^1 = R^2 = Me, R^3 = R^4 = H
1f, 2f: R^1 = Et, R^2 = Me, R^3 = R^4 = H
1g, 2g: R^1 = Pr, R^2 = Me, R^3 = R^4 = H
1h, 2h: R^2 = H, n = 0
1i, 2i: R^2 = H, n = 1
1j, 2j: R^2 = Me, n = 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**

Entry	Substrate	Products		Yield [%]	dr *cis/trans*
a				72	85:15
b				88	51:49
c				96	53:47
d				63	69:31
e				73	71:29
f				63	67:32
g				75	54:45
h				86	12:88
i				97	69:31
j				82	72:28

Experimental

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

A solvent of **1a-j** (1 mmol), Ph_2Se_2 (156 mg, 0.5 mmol), silica gel (150 mg, 5 mmol) and $NaClO_4$ (123.5 mg, 1 mmol) in MeCN (10 ml) was placed in an undivided electrolyses 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 CH_2Cl_2, washed with sat. $NaHCO_3$ solution and brine, and dried over anh. Na_2SO_4. The solvent was evaporated and the reaction mixture was analyzed by TLC and ^{1}H NMR spectroscopy.

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Raferences

1. (a) Thenmozhiyal, J. C.; Wong, P. T.; Chui, W. *J. Med. Chem.*, **47** (2004) 1527; (b) Volonterio, A.; de Arellano, C. R.; Zanda, M. *J. Org. Chem.,* **70** (2004) 216.

2. (a) Moloney, G.P.; Martin, G. R.; Mathews, N.; Milne, A.; Hobbs, H.; Dosworth, S.; Sang, P. Y.; Knight, C.; Williams, M.; Maxwell, M.; Glen, R. C. *J. Med. Chem.* **1999**, *42*, 2504-2526; (b) Somsák, L.; Kovácz, L.; Tóth, M.; Ősz, E.; Szilágyi, L.; Györgydeák, Z.; Dinya, Z.; Docsa, T.; Tóth, B.; Gergely, P. *J. Med. Chem.* **2001**, *44*, 2843-2848; (c) Kaschani, F.; Clerc, J.; Krahn, D.; Bier, D.; Hong, T. N.; Ottmann, C.; Niessen, S.; Colby, T.; van der Hoorn, R. A. L.; Kaiser, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 5230-5233; (d) Nakajima, M.; Itoi, K.; Takamatsu, Y.; Kinoshita, T.; Okazaki, T.; Kawakubo, K.; Shindo, M.; Honma, T.; Tohjigamori, M.; Haneishi, T. *Antibiotics* **1991**, *44*, 293-300.

3. (a) Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293. (b) Fraile, J. M.; Lafuente, G.; Mayoral, J. A.; Pallarés, A. *Tetrahedron* **2011**, *67*, 8639. (c) Wehner, V.; Blum, H.; Kurz, M.; Stilz, H. U. *Synthesis* **2002**, 2023. (d) Pesquet, A.; Daïch, A.; Hijfte, L. V. *J. Org. Chem.* **2006**, *71*, 5303.

4. (a) Alsina, J.; Scott, W. L.; O’Donnell, M. J. *Tetrahedron Lett.* **2005**, *46*, 3131. (b) Albers, H. M. H. G.; Hendrickx, L. J. D.; van Tol, R. J. P.; Hausmann, J.; Perrakis, A.; Ovaa, H. *J. Med. Chem.* **2011**, *54*, 4619. (c) Dhara, K.; Midya, G. C.; Dash, J. *J. Org. Chem.* **2012**, *77*, 8071. (g) Ambrozak, A.; Gütschow, M. *J.*

Heterocyclic Chem. **2006**, *43*, 807. (d) Brockmeyer, F.; Kröger, D.; Stalling, T.; Ullrich, P.; Martens, J. *Helv. Chim. Acta* **2012**, *95*, 1857.

5. (a) Nicolaou, K. C. *Tetrahedron* **1981**, *37*, 4097-4109; (b) Tiecco, M.; Tingoli, M.; Testaferi, L. *Pure App. Chem.* **1993**, *65*, 715-722; (c) Knight, D. W. *Progress in Heterocyclic Chemistry* **2002**, *14*, 19-51; (d) Fugita, K. *Rev. Heteroatom Chem.* **1997**, *16*, 101-117; (e) Petragnani, A.; Stefani, H. A.; Valduga, C. J. *Tetrahedron* **2001**, *57*, 1411-1448; (f) Khokhar, S. S.; Wirth, T. *Eur. J. Org. Chem.* **2004**, 4567-4581; (g) Tiecco, M.; Testaferi, L.; Santi, C. *Eur. J. Org. Chem.* **1999**, 797-803.

6. (a) Šmit, B. M.; Pavlović, R. Z. *Tetrahedron* **2015**, *71*, 1101-1108; (b) Šmit, B. M.; Rodić, M.; Pavlović, R. Z. *Synthesis* **2015**. in press.

7. (a) Röse, P.; Emge, S.; Yoshida, J.; Hilt, G. *Beilstein J. Org. Chem.* **2015**, *11*, 174-183; (b) Stevanović, D.; Pejović, A.; Vukićević, M. D.; Dobrikov, G.; Dimitrov, V.; Denić, M. S.; Radulović, N. S.; Vukićević, R. D. *Helv. Chim. Acta* **2013**, *96*, 1103-1110.

8. Šmit, B. M.; Pavlović, R. Z.; Milenković, D. A.; Marković, Z. S. *Beilstein J. Org. Chem.* **2015**, *11*, 1865-1875.