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Short communication

SHORT COMMUNICATION

Influence of electrochemical conditions on the regio- and stereoselectivity of selenocyclization of alkenyl hydantoins

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Abstract: 5-Alkenyl hydantoins and alkenyl spirohydantoins are converted into bicyclic and tricyclic hydantoins, under indirect electrochemical conditions, generating the phenylselenyl cation *in situ*. The reactions proceeded in good to exelent yields. The influence of electrochemical conditions on regio- and diastereoselectivity of the selenocyclization reactions is investigated.

Keywords: electrosynthesis; constant-current electrolysis; selenylation; ring closure.

INTRODUCTION

The use of electrochemical methods in organic synthesis has become increasingly more popular due to simple procedures and laboratory techniques and the use of cleaner and greener solvents. It is worth noting that the outcomes of the reactions can be vastly different, while some reactions can only be carried out under electrochemical conditions.[1] The hydantoin core represents an important pharmacophore occurring in many biologically active compounds mostly known due to their antimicrobial, anticancer and anticonvulsant activity.[2,3] Spirohydantoins[4] and fused[5] polycyclic hydantoins are the leading compounds in drug discovery, due to their various biological activities. Selenocyclization is a convenient and useful tool for the construction of heterocycles.[6,7] We described a methodology for the synthesis of bicyclic and tricyclic fused hydantoin scaffold, using selenocyclization for the construction of sterically constrained structures that have potential in peptidomimetic drug design.[8,9] In this work we decided to use the electrochemically generated phenylselenyl cation in the cyclization of 5-alkenyl hydantoins and alkenyl spirohydantoins and explore whether these condit-

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ions have an effect on the course of the reaction, especially on regio- and stereoselectivity.

EXPERIMENTAL

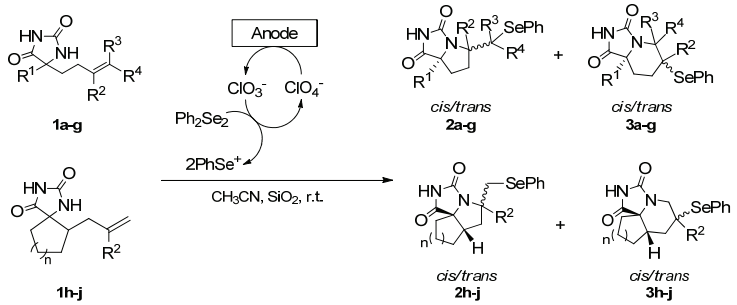
General. All alkenyl hydantoins used as substrates were synthesized according to the procedures described previously.[8] Reagent Ph_2Se_2 was used as supplied by Aldrich. Gas–liquid chromatography (GLC) was performed by Varian instument model 3400. ^{1}H-NMR spectra were run in $CDCl_3$ on a Varian Gemini 2000 spectrometer at 200 MHz.

*General procedure for the electrochemical selenocyclization of hydantoins (**1a**–**j**).* A solution 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 electrolysis cell and electrolyzed under a constant current (10 mA) at room 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 GLC and ^{1}H-NMR spectroscopy.

RESULTS AND DISCUSSION

The alkenyl hydantoins contain a double bond and an internal nitrogen nucleophile, and they are suitable substrates for the 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.[10,11]

The cyclization of the previously synthesized 5-alkenyl hydantoins **1a**–**g** and alkenyl spirohydantoins **1h**–**j** was performed by the means of electrochemically generated phenylselenyl cation, which originates from diphenyldiselenide in a MeCN solution of $NaClO_4$ (Scheme 1). Perchlorate in this process serves as a mediator. Before that, we tried to perform the reaction of the commercially available product **1d**, with other supporting electrolytes (LiCl, KCl, NaBr, KI), solvents and electrodes, but $NaClO_4$ in MeCN and C–Pt electrodes gave the best results (Table I, Entry 6).



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 = 1
1i, 2i: R^2 = H, n = 2
1j, 2j: R^2 = Me, n = 2

Scheme 1. Selenocyclization of alkenyl hydantoins **1a**–**g** and alkenyl spirohydantoins **1h**–**j**.

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TABLE I. Optimization of electrochemical conditions for the cyclization reaction of **1d**

Entry	Anode–cathode	Supporting electrolyte	Solvent	Overall yield[a] (6/5), %	Diasteromeric ratio[a] *cis*/*trans*, %
1	Pt–Pt	KCl	CH_3CN	10	78:21
2	Pt–Pt	NaBr	CH_3CN	6	–
3	Pt–Pt	KI	CH_3CN	5	75:25
4	Pt–Pt	$NaClO_4$	CH_3CN	31	62:38
5	Pt–Pt	$NaClO_4$	CH_3CN	4	–
6	C–Pt	$NaClO_4$	CH_3CN	63 (46:54)	6(59:41); 5(69:31)
7	C–Cu	Et_4NBr	CH_3CN	1	–
8	C–Cu	$NaClO_4$	CH_3CN	47 (68:32)	6(51:49); 5(7:93)
9	C–Cu	LiCl	CH_3CN	traces	–
10	C–Cu	KI	CH_3CN	34 (42:58)	6(52:48); 5(72:28)
11	C–Pt	$NaClO_4$	CH_2Cl_2:CH_3CN=2:1	Traces	–
12	C–Pt	$NaClO_4$	Py:CH_3CN=1:1	Traces	–
13	C–Pt	$NaClO_4$	Toluene:CH_3CN=2:1	57 (83:17)	6(48:52); 5(84:16)
14	C–Pt	$NaClO_4$	THF	Undetectable	–
15	C–Pt	$NaClO_4$	Ethanol	Undetectable	–
16	C–Pt	$NaClO_4$	DMF	Traces	–

[a]Ratio of regio and diastereoisomers are obtained from GLC and ^{1}H-NMR spectra

The easy oxidation of perchlorate at the anode provides *in situ* generation of $PhSe^+$ able to react with the π-electron system of the substrate. The reaction yields products resulting from the nucleophilic attack of the nitrogen atom to the cyclic seleniranium ion intermediate during the cyclization step.

Under the chosen reaction conditions, a series of alkenyl hydantoins **1a**–**j** was subjected to electrochemical selenocyclization (Table II). In the previously reported results,[8,9] the reaction was regiospecific and 5-membered regioisomers were formed *via* favorable *5-exo-trig* ring closure process which is both kinetically and thermodynamically favoured.[12] Products where the bridgehead substituent and CH_2SePh group are in *cis* positions one to another were formed predominantly. In contrast, when the phenylselenyl cation is electrochemically generated *in situ*, it was noticed that the regio- and diastereoselectivity both depend on the steric hindrance at C-5 of the hydantoin ring and the C-C double bond. 5-*Exo-trig* cyclization products are also obtained regiospecifically in most cases, but with poorer stereoselectivity. The amount of *trans*-diastereoisomers is increased in comparison to the previous results, implying higher thermodynamic control of the cyclization process. Exceptions are the cyclizations of **1c** and **1j** where the steric hindrance is most pronounced and the kinetic control is favoured, increasing the *cis*-selectivity. Only in the absence of steric hindrance in the starting alkenyl hydantoin, 6-membered regioisomers are formed *via* 6-*endo*-*trig* ring closure process. In the case of **1a**, where a methyl group is attached on C-5 and the double bond is unsubstituted, the six-membered regioisomer is obtained almost exclusively and as a *trans*-isomer stereospecifically. Six-mem-

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bered product is also obtained in the cyclization of **1d,** where a methyl group is attached on C5 and the double bond is terminally disubstituted, but without regio- and stereoselectivity. When the double bond is non-terminally substituted, like in **1e**, despite having a methyl group attached on C-5, the six-membered regioisomer is not formed at all. It is assumed that the methyl group on the double bond directly hinders the approach of seleniranium cation to the nitrogen atom during cyclization. Regardless of the substitution of the double bond, the cyclization of alkenyl spirohydantoins **1h**–**j** depends on the size of the cycloalkyl group. The product of *6-endo-trig* ring closure occurs predominantly only in the case of **1h** without any stereocontrol, while the minor product of 5-*exo-trig* ring closure occurs with the reversed stereoselectivity compared to results reported previously.[9] The bulkier six-membered ring in **1i** and **1j** presumably prevents the formation of another six-membered ring.

TABLE II. Selenocyclization of alkenyl hydantoins **1a**–**g** and alkenyl spirohydantoins **1h**–**j**

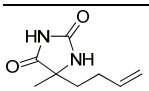
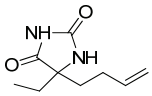
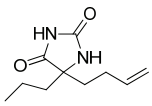
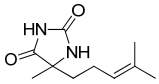
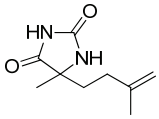
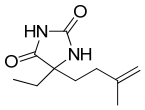
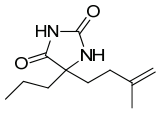
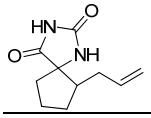
Substrate	Yield, %	Regioisomer ratio[a] **2**:**3**	dr (*cis*/*trans*)[a] **2**	dr (*cis*/*trans*)[a] **3**
	72	1:99	–	0:100
	88	100:0	70:30	–
	96	100:0	71:29	–
	63	54:46	69:31	59:41
	73	100:0	56:44	–
	63	100:0	44:56	–
	75	100:0	48:52	–
	86	35:65	24:76	50:50

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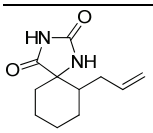
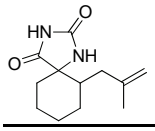
TABLE II. Continued

Substrate	Yield, %	Regioisomer ratio[a] **2**:**3**	dr (*cis*/*trans*)[a] **2**	dr (*cis*/*trans*)[a] **3**
	97	100:0	68:32	–
	82	100:0	100:0	–

[a]Ratio of regio- and diastereoisomers are obtained from GLC and ^{1}H NMR spectra

CONCLUSION

The influence of electrochemical conditions on selenocyclization reactions of alkenyl hydantoins and spirohydantoins has been explored. Various different solvent/mediator systems have been taken into consideration and MeCN/$NaClO_4$ showed the best results. Steric hindrances in the starting alkenyl hydantoins influence the regio- and the stereochemical outcome of the reactions and in these conditions thermodynamic control is more present.

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ИЗВОД

УТИЦАЈ ЕЛЕКТРОХЕМИЈСКИХ УСЛОВА НА РЕГИО- И СТЕРЕОСЕЛЕКТИВНОСТ СЕЛЕНОЦИКЛИЗАЦИЈЕ АЛКЕНИЛХИДАНТОИНА

БИЉАНА М. ШМИТ[1], ПЕТАР Б. СТАНИЋ[1], ЉУБИНКА Г. ЈОКСОВИЋ[2], ДАРКО П. АШАНИН[1] и ЗОРАН СИМИЋ[2]

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5-Алкенилхидантоини и алкенилспирохидантоини су преведени у бицикличне и трицикличне хидантоине под индиректним електрохемијским условима при којима се фенилселенил-катјони стварају *in situ*. Реакције су се одигравале у добрим до одличним приносима. Испитиван је утицај електрохемијских услова на регио- и дијастереоселективност реакција селеноциклизације.

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