Synthesis of fused tricyclic hydantoins of homotriquinane type

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Abstract: Synthesis of tricyclic hydantoins with angularly fused rings was performed in three-step reaction sequence. Spiro-bicyclic hydantoins with alkenyl moiety, prepared from 2-alkenylcyclohexanones using Bucherer-Bergs reaction, were subjected to amidoselenylation reaction. This selenium-induced intramolecular cyclization is a key step of this sequence. The cyclization is regiospecific and formation of sole regioisomer proceeds via favorable *5-exo-trig* ring closure process giving only homotriquinane type tricyclic hydantoins.

Key words: hydantoins, intramolecular cyclization, selenium, fused rings

Introduction

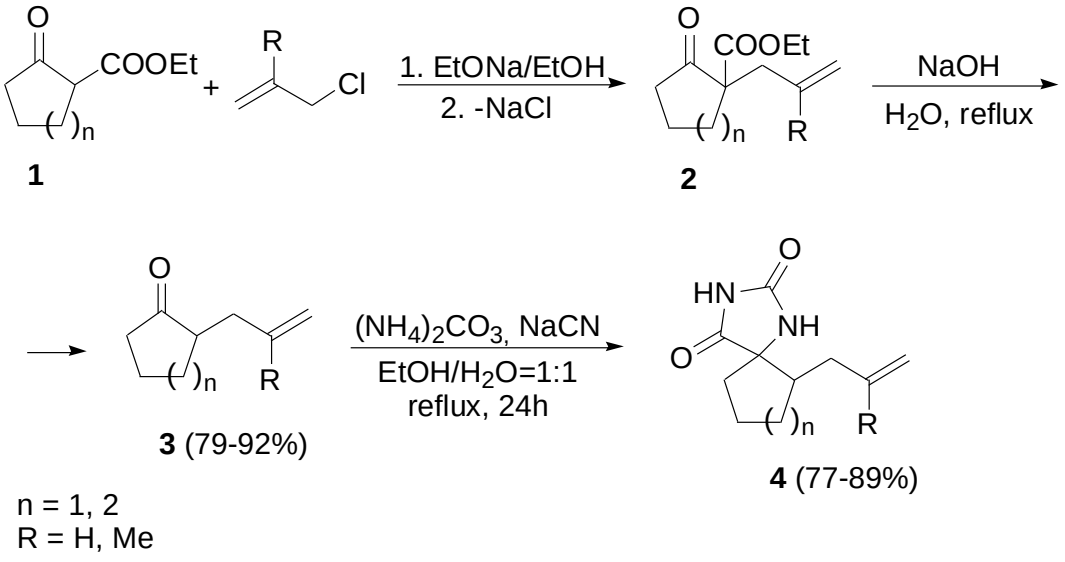
Hydantoins are important moieties found in numerous natural products[1,2]. Hidantoin-based scaffolds often show interesting and significant pharmacological activities[3]. Spirohydantoins[4] and fused polycyclic hydantoins[5] have attracted much attention in medicinal chemistry but there exist very few methods for their synthesis[6]. Therefore, the development of efficient and elegant synthetic strategies for the

preparation of new functionalized hydantoin derivatives would be highly desirable due to their similarity with drug-like molecules.

In continuation to our previous work[7], in this paper we describe the using of selenocyclization of alkenyl spirohydantoins for the synthesis of fused tricyclic hydantoins. These products are unique tricyclic scaffolds reminiscent of angular triquinanes. They are assembled in a four-step reaction sequence from two variable building blocks by combining Bucherer-Bergs reaction with a final intramolecular selenocyclization.

Results and discussion

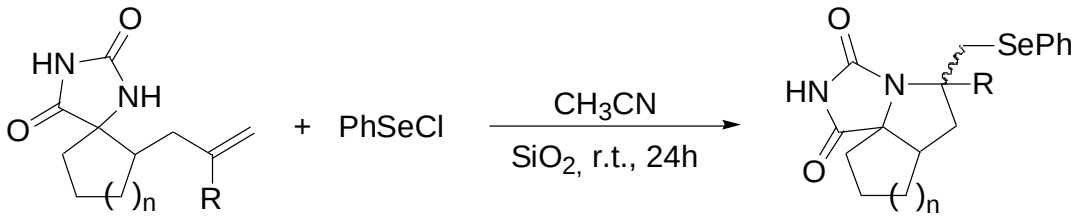
For our study, readily available cyclic β-ketoesters **1a,b** (n=1,2) were subjected to carbanionic alkenylation to perform alkenylated cyclic β-ketoesters **2a-c (**Scheme 1). After subsequent decarbethoxylation cyclic ketones with alkenyl moieties **3a-c** were obtained in good yield.



Scheme 1. Synthetic pathway for the preparation of alkenyl spirohydantoins

For the preparation of 5-alkenyl hydantoins, we have chosen the use of the well-established Bucherer-Bergs reaction[8]. Under these conditions compounds **4a-c,** as crystalline solids, were obtained in good yields (Scheme 1).

The resulting alkenyl spirohydantoins contain a double bond and an internal nitrogen nucleophile, and they could be suitable substrates for intramolecular electrophilic cyclization. In the final step, alkenyl spirohydantoins were submitted to the selenium-induced cyclization reaction giving, in overall four-step sequence, fused tricyclic hydantoins **5a-c** in high yield (Scheme 2, Table 1).



4 **5**

Scheme 2. Selenocyclization of alkenyl spirohydantoins

Table 1. Selenocyclization of alkenyl spirohydantoins

Substrate	n	R	Products	Yield [%][b]	d. r.[c]
4a	2	H	**5a**	89	94:6
4b	2	Me	**5b**	95	67:33
4c	1	H	**5c**	92	55:45

[a]The reactions were conducted using 2.5 mmol of SiO_2, 0.55 mmol of PhSeCl and 0.5 mmol of alkenyl spirohydantoin (**4a-c**) in acetonitrile (5 mL). [b]Isolated yield. [c]Determined from ^{1}H NMR spectra of crude reaction mixture.

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. The products obtained by cyclization of **4a** and **4b** are fused tricyclic hydantoins of homotriquinane type (**5a** and **5b**), while **5c** has angularly fused triquinane-type core of the axinellamines[9].

The cyclization of spirohydantoin cyclohexane intermediates proceeded in stereoselective manner obtaining the separable diastereomeric mixture. In contrast, the cyclization of cyclopentane intermediate was not selective. The observed diastereomeric ratios and chemical yields are summarized in Table 1. A detailed structural analysis and relative stereochemical assignments have not been yet complete.

Conclusion

In summary, we have demonstrated an elegant and straightforward regioselective selenocyclization of alkenyl spirohydantoin cyclopentane and cyclohexane intermediates that efficiently deliver the angularly fused tricyclic hydantoins. These novel compounds share the structural complexity characteristic to certain alkaloid natural products and represent a source of chemical diversity that complements more traditional classes of heterocyclic compounds of interest as potential pharmaceutical agents.

Experimental

General procedure for alkenylation of β-ketoesters

β-Ketoester **1** (60 mmol) was added to a stirred solution of sodium ethoxide (prepared from metallic sodium (1.380 g (60 mmol), cut into pieces and added to anhydrous ethanol (40 mL)), at room temperature. After stirring for 1 h alkenyl chloride (allyl or methallyl chloride (60 mmol)) was added dropwise over a period of 30 min. The mixture was heated at reflux until the litmus test showed a neutral reaction (3-5 h). The reaction mixture was cooled to room temperature and poured into water (25 mL) and the aqueous layer was separated and extracted with Et_2O (4×15 mL). The combined organic phases were dried (Na_2SO_4), filtered, concentrated in vacuo and distilled under reduced pressure to give the desired alkenyl β-ketoesters as transparent oil.

General procedure for decarbethoxylation of 2-alkenyl β-ketoesters. Preparation of unsaturated ketones

Alkenyl β-ketoesters (20 mmol) were heated in aqueous sodium hydroxide (2.400 g in 30 mL deionised water) for 2 h at reflux. Reaction mixture was cooled to r.t. and

extracted with diethyl ether (3×20 mL). The combined ether extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue that was distilled under reduced pressure to give the desired unsaturated ketones.

General procedure for preparation of 5-alkenyl hydantoins (3a-i)

To a 100 mL round bottom flask equipped with reflux condenser, 5 mmol unsaturated ketone, 0.490 g NaCN (10 mmol) and 1920.0 mg (20 mmol) $(NH_4)_2CO_3$ were added to 30 mL of 50% aqueous solution of EtOH. The reaction mixture was stirred and heated to reflux for 24 h. The reaction mixture was then cooled to ambient temperature and filtered off. The pH of filtrate was adjusted to ∼2 by carefully adding of conc. HCl. The filtrate was placed in a refrigerator for better crystallization of the products. The products were separated by filtration.

General procedure for synthesis of tricyclic hydantoins (4a-k)

To a 50 mL round bottom flask 150 mg (2.5 mmol) of SiO_2, 105.4 mg (0.55 mmol) of PhSeCl and 0.5 mmol of alkenyl hydantoin (**3a-k**) were dissolved in acetonitrile (5 mL). Reaction mixture was stirred at ambient temperature for 24 h. Dichlormethane (20 ml) was then added and mixture was filtered to remove SiO_2. Filtrate was washed with saturated solution of $NaHCO_3$, 5% solution of NaCl and dried over anhydrous Na_2SO_4 for 8 h. Neutral mixture of products was analyzed by thin-layer chromatography and ^1H NMR. Filtrate was evaporated under reduced pressure and products were isolated by column chromatography on silica gel (hexane/EtOAc) or cristallization.

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