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The authors have full responsibility for the originality and content of their own papers.

INTRAMOLECULAR AMIDOSELENYLATION IN THE SYNTHESIS OF CONSTRAINED UNNATURAL AMINO ACIDS

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ABSTRACT:
In this paper use of intramolecular electrophilic amidoselenylation of unsaturated hydantoins for the construction of annulated bicyclic hydantoins, conformationally constrained precursors of substituted prolines is presented. In the case when alkenyl spirohydantoins were used as the substrates for amidoselenylation angularly fused tricyclic hydantoins are obtained. Reductive deselenylation and hydrolytic opening of the hydantoin ring of these products lead to fused bicyclic prolines, quaternary and constrained unnatural amino acids which can find application as peptidomimetics and also as intermediates in the synthesis of some natural products. Amidoselenylation of same substrates was also performed with in situ electrochemically generated selenium reagent. The reactions tolerate different substitutions at the unsatutated moiety and gave access to vide variety of derivatives.

Keywords: *amidoselenylation, cyclization, unnatural amino acids, peptidomimetics*

1. INTRODUCTION

Conformationally constrained monocyclic [1] and bicyclic [2] unnatural amino acids are of valuable interest as versatile molecules used in a wide range of applications in different fields. Their incorporation into a native peptide or peptido-mimetics induces conformational restriction and provides significant structural effects that can lead to compounds, which may improve efficiency, selectivity toward a specific receptor, resistance to chemical, and enzymatic degradation, and thus the bioavailability. [3] The unique potential of sterically constrained amino acid [4] in the structure-based peptidomimetic drug design [5] has generated a considerable effort directed toward the development of efficient methods for their preparation. Cyclic residues and quaternary α-amino acids have gathered special interest due to their ability to restrict the ψ, φ, and ω torsional angles of the peptide backbone. Among proteinogenic amino acids, proline takes a special place due to its unique structure. The nitrogen atom, incorporated in a five-membered ring, effects conformational changes compared to other natural amino acids. These features are more pronounced for amino acids possessing a further strained ring. Proline confers conformational restrictions to peptides, [6] which can induce the formation of β- and γ-turns, hence its replacement with analogues can provide additional insight about receptor recognition and affinity. Thus, much effort has been devoted towards the exploration of structural variants carrier of higher conformational constraint and chemical diversity. [7] The synthesis and application of fused bicyclic α-amino acids, especially the sub-group of bicyclic proline analogues, have received much attention

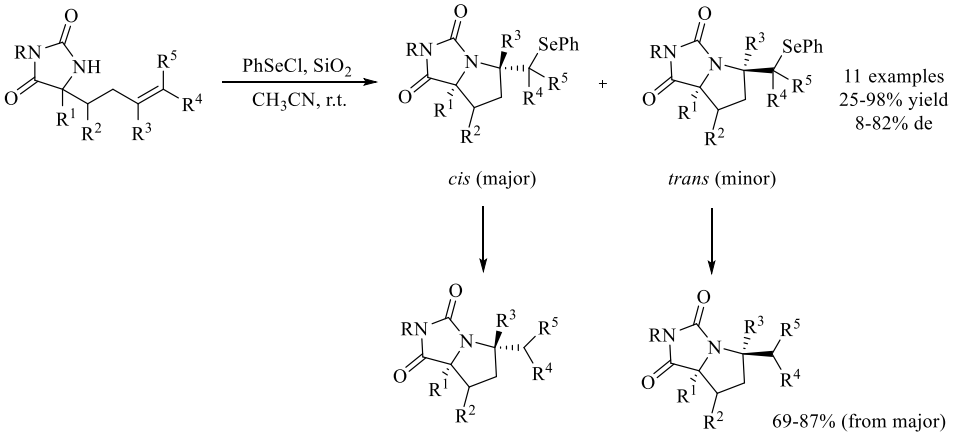
in recent years. [8,9] In particular, synthetic approaches have been reported for the construction of bicycles having ring junctions at different positions of the proline ring. [10]

2. HYDANTOINS AS PRECURSORS OF α-AMINO ACIDS

Imidazolidine-2,4-dione derivatives, generally called hydantoins, [11] are class of cyclic ureides which exhibit diverse biological activity and, therefore, considered as attractive lead compounds in medicinal chemistry and drug discovery. [12] 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 bicyclic hydantoin derivatives have recently attracted much attention in drug discovery due to their various biological activities. Further, hydantoins are important class of compounds because of their industrial relevance as intermediates in the production of α-amino acids. Herein, we report the synthesis of the precursors of higly substituated quaternary prolines and conformationally restricted bicyclic proline analogues, which might be used as excellent building blocks for constrained peptidomimetics.

2.1. Selenocyclization of 5-alkenyl hydantoins

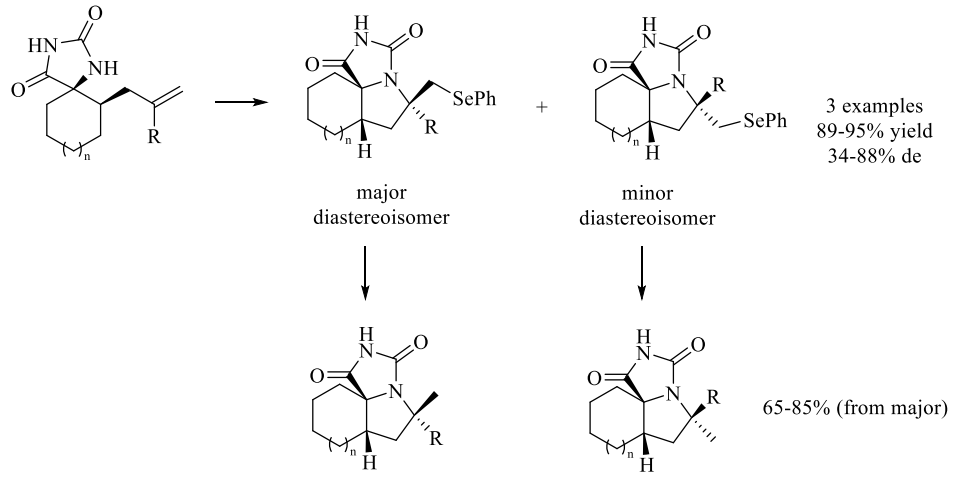
Selenocyclization proved to be a powerful and versatile tool for the construction of heterocyclic rings. [13] Its use for the construction of pyrrolidine rings has been well established. Herein, we describe a new methodology for the synthesis of a bicyclic hydantoin scaffold and our independent efforts to exploit intramolecular selenocyclization for fashioning molecules having rigid, conformationally well-defined structure consistent with attractive lead compounds for drug discovery.
Intramolecular electrophilic amidoselenylation of 5-alkenyl-hydantoins was used for the construction of fused bicyclic hydantoins, conformationally constrained precursors of substituted prolines. The reaction proceeded in mild conditions, giving regioselectively Markovnikov-type of products through a *5-exo-trig* cyclization in moderate to excellent yields (Scheme 1). Fused bicyclic hydantoins with bridgehead substituents and phenylseleno groups in *cis* configuration were obtained predominantly with moderate to good diastereomeric ratios. The reaction tolerates different substitutions at the olefinic bond and gave access to derivatives with broad structural variety. [14] Mechanism, kinetics and selectivity of this selenocyclization are investigated by experimental (^{1}H NMR spectroscopy) as well as theoretical (DFT) methods. [15] The proposed mechanism implies at first addition of selenium reagent on double bond prior to cyclization. Cyclization proceeded through an *anti*-attack of nucleophilic amidic nitrogen to seleniranium cation forming pyrrolidine ring which is *cis*-fused with hydantoin nucleus. Reaction is both kinetically and thermodynamically controlled and proceeds via favorable *5-exo-trig* ring closure process. Reductive deselenylation affords saturated bicyclic hydantoins, precursors of quaternary and highly substituted proline derivatives.



Scheme 1. Selenocyclization of 5-alkenyl hydantoins.

2.2. Selenocyclization of alkenyl spirohydantoins

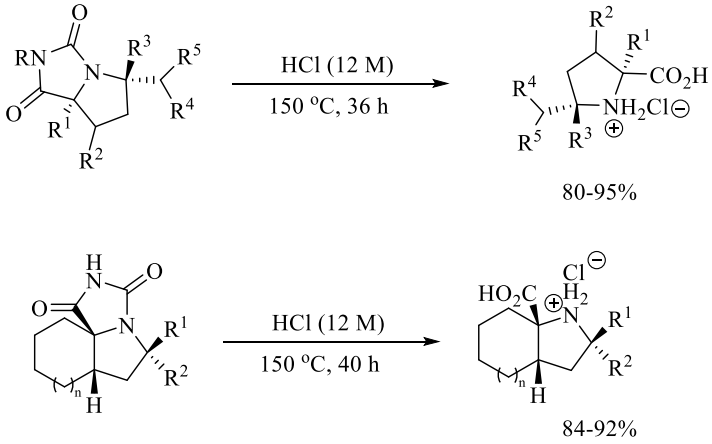
When alkenyl spirohydantoins were used as the substrates for amidoselenylation angularly fused tricyclic hydantoins having α,β-ring junction are obtained in excellent yields with moderate to high distereoselectivity. [16] Upon hydrogenation of the tricyclic selenohydantoins over Raney Ni in THF deselenylated saturated tricyclic products, precursors of conformationally constrained bicyclic proline derivatives, were obtained in good to excellent yields. (Scheme 2).



Scheme 2. Selenocyclization of alkenyl spirohydantoins

2.3. Hydrolysis of bicyclic and tricyclic hydantoins to proline derivatives

Synthesized angularly fused bicyclic hydantoins are valuable precursors of substituted quaternary α-amino acid proline. Acid hydrolysis of these compounds leads to the highly substituted proline derivatives with five points of diversity (Scheme 3).
Angularly fused tricyclic hydantoins are suitable precursors of *cis*-fused bicyclic α-amino acids. Moreover, they can be easily converted into corresponding fused bicyclic α-prolines (Scheme 3). Hydrolytic opening of hydantoin ring of these products lead to fused bicyclic α-prolines with three points of diversity (size of cycloalkyl ring and substituents at the pyrrolidine ring). This methodology is suitable for large-scale production of highly constrained quaternary bicyclic α-prolines with different ring sizes.
These quaternary and constrained unnatural amino acids can find application as peptidomimetics and also as intermediates in the synthesis of some natural products. Angularly fused (homo)triquinane-type hydantoins posses tricyclic core of complex pyrrole-imidazole alkaloids axinellamines and massadine.



Scheme 3. Hydrolysis of angularly fused bicyclic and tricyclic hydantoins to α-proline derivatives

3. CONCLUSION

In conclusion, we have demonstrated a highly efficient method for the preparation of angularly fused bicyclic and tricyclic hydantoins, in good to excellent yields, including an intramolecular electrophilic amidoselenylation of alkenyl hydantoins. The excellent chemo- and regioselectivity are important advantages of this method which furnishes molecules which diversity can be directed by the choice of starting materials during the synthesis of alkenyl hydantoins. Thus, we have an easy access to azabicyclic compounds bearing nitrogen at the fusion of five-membered rings, which are key building blocks in many multistep alkaloids and drug syntheses. Due to the presence of the carbonyl and phenylselenium groups, these products can be employed for further interesting transformations. Furthermore, substituted α-proline derivatives could be obtained by hydrolytic opening of hydantoin ring. This methodology is suitable for large-scale production of highly constrained quaternary prolines as well as bicyclic prolines with different ring sizes.

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