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Straightforward synthesis of non-natural chalcogen peptides via ring opening of aziridines

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ABSTRACT

The synthesis of new chiral non-natural seleno-, thio-, and telluro-peptides is described herein. These new compounds were prepared through simple and brief synthetic route, from inexpensive and commercially available amino acids. The products, possessing a highly modular character, were obtained in good to excellent yields (50–96%), via ring opening of aziridines with chalcogenolate anions, generated using indium(I) iodide as a reducing agent.

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1. Introduction

The interest in synthesizing small molecules that mimic the structures of bioactive peptides has become an important goal in synthetic organic chemistry.[1] A special emphasis has been given to the replacement of natural amino acids in peptides for non-proteinogenic derivatives in order to obtain drug-like target molecules.[2] Moreover the interest in the biological and medicinal properties of selenium and organoselenium compounds is also increasingly appreciated, mainly due to their antioxidant, antitumor, antimicrobial, and antiviral properties.[3] This increasing interest has attracted considerable attention in the development of new organoselenium compounds. In this context, synthetic methods for the preparation of selenocysteine,[4] selenium based peptides,[5] selenoglycosides,[6] selenonucleosides,[7] seleno-carbohydrates,[8] and other important natural coumpounds[9] are currently an area of intensive research.

Among selenium and tellurium compounds, the chalcogen amino acids have emerged as an exceptional class of structures in recent years, due to their interesting biological properties, such as selenocysteine, selenomethionine and the analogous tellurium compounds, in which the amino acid side chain is isosteric with cysteine or methionine.[10] Many selenoenzymes have a selenocysteine residue at the active site as a catalyst for various redox reactions.[11] Perhaps the most important and studied enzyme is glutathione peroxidase (GPx), which protects the body against the potentially damaging effects of reactive oxygen species formed during aerobic metabolism.[12] Several neurodegenerative diseases, including Alzheimer's, Parkinson's and other physiological and inflammatory processes are associated with oxidative stress.[13] Since the discovery that selenium plays a pivotal role in GPx enzymes, synthetic developments toward design of new chalcogen based catalytic antioxidants have attracted considerable attention.[3a,14] In this context, novel compounds derived from amino acids containing chalcogen atom have arisen as excellent candidates for GPx mimics.[15]

Chalcogen-containing peptides offer attractive and practical potential toward the development of new ligands for asymmetric transformations.[16] Further, they are easily prepared from readily available, modular chiral building blocks.

On the other hand, chiral aziridines are one of the most versatile three-membered ring systems in modern synthetic chemistry.[17] They constitute a useful class of nitrogen-containing compounds and are also key intermediates for the regiocontrolled introduction of a chalcogen atom in the product. In this context different β-seleno amines and selenocysteine derivatives have been prepared via ring opening of aziridines with chalcogen nucleophiles, generated by reducing agents, such as $NaBH_4$, $LiBHEt_3$, Zn, rongalite and KOH/CuO.[18] In recent years our group developed an indium (I) protocol for the preparation of selenocysteine derivatives through the ring opening of aziridine-2-carboxylate. By this method, a series of

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selenoamino acids could be synthesized in good to excellent yields.[19] In this work we discovered that when the selenolate anion was generated using $NaBH_4$/EtOH the reaction failed to prepare selenocysteine derivatives. Notably, indium selenolate promoted faster aziridine ring opening in the absence of a Lewis acid (Fig. 1).

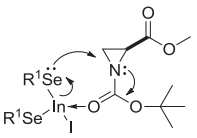
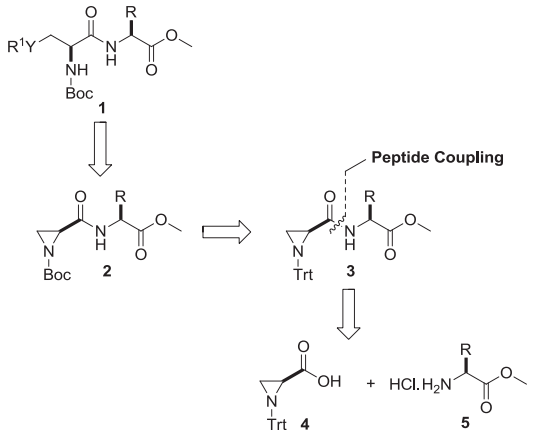


Fig. 1. Proposed mechanism for the aziridine ring opening.

In this context, and as a part of our growing interest in chalcogen compounds,[20] we describe herein an easy, inexpensive and straightforward synthetic route for the preparation of a series of non-natural chalcogen peptides. Our approach to the preparation of these new *N*-Boc chalcogen peptides took advantage of our previous protocol,[19] and consisted of a ring opening reaction of aziridine by indium chalcogenolate anions as depicted in the proposed retrosynthetic analysis (Scheme 1). For the preparation of the key aziridines, we selected some procedures already described in the literature, which explores the preparation of these aziridines starting from common available amino acids.

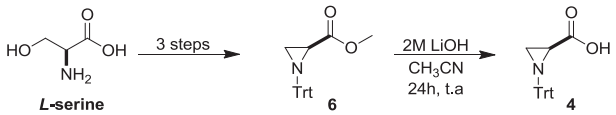


Scheme 1. Retrosynthetic analysis for chalcogen peptides **1**.

2. Results and discussion

According to our objectives and as the starting point for the synthesis of chalcogen peptides **1** we had to devise an efficient method of preparation for chiral *N*-Boc-aziridines **2** in a short and high yielding sequence. To accomplish this task we used methodologies already described in the literature.

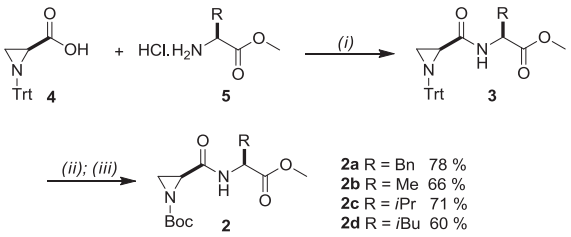
Following the protocol previously reported, the (*S*)-methyl 1-tritylaziridine-2-carboxylate **6** was prepared in high yields starting from L-serine.[21] In the next step the hydrolysis of methyl ester was achieved by reaction with 2 M lithium hydroxide in acetonitrile affording (*S*)-1-tritylaziridine-2-carboxylic acid **4** in 91% yield (Scheme 2).[22]



Scheme 2. Synthesis of (*S*)-1-tritylaziridine-2-carboxylic acid **4** from L-serine.

With the (*S*)-1-tritylaziridine-2-carboxylic acid **4** in hand, we turned your attention toward coupling with L-amino esters **5**. To accomplish this transformation, we chose the mixed anhydride method.[23] Coupling conditions consisted of treatment of the (*S*)-1-tritylaziridine-2-carboxylic acid **4** with *N*-methylmorpholine in chloroform, followed by the addition of ethyl chloroformate to afford the mixed anhydride in situ, which was then treated with L-amino esters **5** and other equivalent of *N*-methylmorpholine to form the amide bond (Scheme 3). A series of compounds was synthesized through variation of the amino ester residues. Compounds of type **3** were submitted to a short purification over silica gel to remove the unreacted starting materials.

In order to facilitate an efficient ring opening of the aziridine, it was necessary to replace the trityl group with an electron withdrawing group, such as *tert*-butoxycarbonyl (Boc). Following the protocol reported in the literature,[24] the protecting group interconversion **3**→**2** was achieved using a one-pot strategy in order to avoid the isolation of the intermediate free aziridines. Hence, removal of trityl group from **3** using trifluoroacetic acid, basification with excess of triethylamine and in situ reprotection with Boc_2O gave the *N*-Boc aziridines **2a**–**d** in good yields (Scheme 3).



Scheme 3. Synthetic strategies to prepare *N*-Boc aziridines **2a**–**d**. Reagents and conditions: (i) NMM, ethyl chloroformate, NMM, $CHCl_3$, 0 °C, then 24 h rt; (ii) TFA, MeOH, CH_2Cl_2, 0 °C, 30 min (iii) Et_3N, Boc_2O, 0 °C, then 15 h rt.

It is worth noting that we did not observe any epimerization at the original chiral center from **4**. This result was confirmed through the synthesis of a racemic aziridine *rac*-**4**, which was coupling with L-amino ester of alanine, followed by the removal of trityl group and in situ reprotection with Boc_2O to afford a mixture of diastereoisomers **2b**. By the comparison of both spectra of ^1H NMR, we could then confirm the absence of epimerization, since only a single set of signals was observed for an enantiomerically pure *N*-Boc aziridine **2b**, when compared with a mixture of diastereoisomers **2b** (see Supplementary data).

With the *N*-Boc aziridines **2a**–**d** in hand, we promoted the insertion of the organochalcogen moiety through the nucleophilic ring opening with different selenium anions. To accomplish this task the selenium nucleophile was generated by reduction of diphenyl diselenide with sodium borohydride in a mixture of THF and ethanol. However, under these conditions the ring opening of aziridine **2a** failed and the product was not obtained. This result is in agreement with those previously reported in the literature for a similar aziridine.[19] Attempting to solve this problem we decided to use our protocol, which employs indium (I) iodide to promote the cleavage of diorganoyl diselenides.[19] According to that, indium (I) iodide undergoes an oxidative insertion into a suitable substrate, generating the complex bis(organoylseleno)iodoindium (III). This complex is readily prepared by reacting equimolar amounts of InI and R^1SeSeR^1 in dichloromethane (Scheme 4).

As outlined in the sequence below, the preparation of chalcogen peptides proceeds through the regioselective nucleophilic attack of the organoselenolate anion at the less hindered carbon of the aziridine ring.

After optimization of the reaction conditions, several aziridines and diorganoyl dichalcogenides were applied in order to check the

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