JOC Notes

Chiral Seleno-Amines from Indium Selenolates. A Straightforward Synthesis of Selenocysteine Derivatives

Antonio L. Braga,* Paulo H. Schneider,‡ Marcio W. Paixão, Anna M. Deobald, Clovis Peppe, and Diana P. Bottega

Departamento de Química, Universidade Federal de Santa Maria, Santa Maria, RS, 97105-900, Brazil

albraga@quimica.ufsm.br

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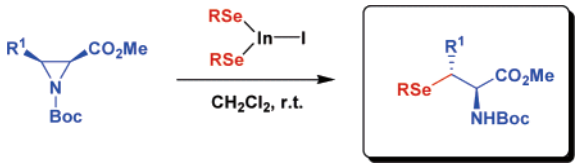
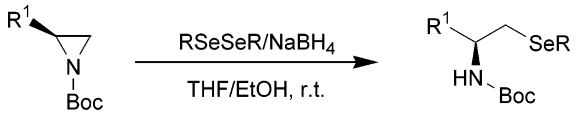


A simple and efficient procedure for the synthesis of chiral β-seleno-amines derivatives from a one-pot indium(I) iodide-mediated aziridine ring opening with diorganoyl diselenides has been developed. As an application, the synthesis of selenocysteine and selenotreonine derivatives has been accomplished.

In recent years interest in selenocystein and its derivatives has extremely increased as they are building blocks for the synthesis of selenoproteins[1] and due to their potential biological activity. The biological and medicinal properties of selenium and organoselenium compounds are increasingly appreciated, mainly due to their antioxidant, antitumor, antimicrobial, and antiviral properties.[2] In addition, selenocysteine derivatives can serve as convenient precursors to dehydroamino acids,[3] which are useful electrophilic handles for the chemoselective preparation of peptide conjugates.[4]

The development of new methods for the introduction of selenium-containing groups into organic molecules, particularly in a stereocontrolled manner, remains a significant challenge.

SCHEME 1. Aziridine Ring Opening with Sodium Selenolate Anions



Yield: 65-90%

Reduction of Se−Se bonds, especially cleavage of diphenyl or diaryl diselenides, has recently received much effort for the preparation of unsymmetrical diorganyl selenides. Chemical cleavage of Se−Se bonds in diaryl diselenides was realized with reducing agents such as $NaBH_4$, Na/NH_3, Bu_3SnH, and $LiAlH_4$.[5] In recent years, some protocols with indium(I) iodide-mediating cleavage of diorganyl diselenides have been developed to prepare vinylic selenides,[6] selenoesters,[7] and β-hydroxy selenides[8] with special attention given to unsymmetrical diorganyl selenides.[9]

In this context, we recently reported the synthesis of a new set of chiral α-seleno-amines in a straightforward manner through the stereoselective aziridine ring opening with selenolate anions (Scheme 1).[10] In this work, the selenium nucleophile required to open the aziridine ring was generated by reduction of the diselenide with sodium borohydride in protic solvent. However, this reaction failed to prepare selenocysteine derivatives through the ring opening of functionalized aziridine.

Attempting to disclose further extension of this work, we examine here the reaction between the indium(III)-chalcogenolates, obtained from indium(I) iodide and diorganyl diselenides, and several types of aziridines. The work resulted in an efficient and mild synthesis of α-seleno-amines and selenocysteine derivatives under mild and neutral conditions. It is well-known that indium(I) compounds, through their oxidative insertion into a suitable substrate, generate the corresponding indium(III) derivative. Thus, the complex bis(organoylseleno)iodoindium-(III), **1**, is readily prepared by reacting equimolar amounts of

* Author to whom corresponding should be addressed. Phone: +55-55-3220-8781. Fax +55-55-3220-8998.

‡ Universidade Federal do Rio Grande do Sul.

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SCHEME 2. Indium(I) Iodide-Mediated Aziridine Ring Opening with Diorganoyl Diselenides

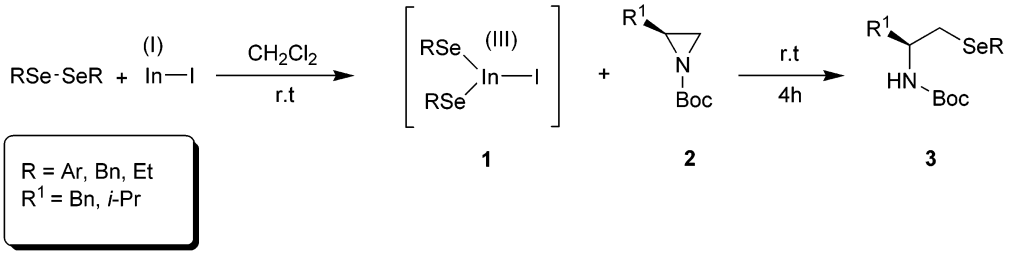


TABLE 1. Ring-Opening Reaction of Aziridine

2a: R^1 = Bn
2b: R^1 = *i*-Pr

entry	R^1	R	product	solvent	isolated yield (%)
1	Bn	Ph	**3a**	THF	65
2	Bn	Ph	**3a**	EtOH	56
3	Bn	Ph	**3a**	CH_3CN	87
4	Bn	Ph	**3a**	DCM	94
5	*i*-Pr	Ph	**3b**	DCM	77
6	Bn	*p*-MePh	**3c**	DCM	85
7	Bn	*p*-ClPh	**3d**	DCM	90
8	Bn	Bn	**3e**	DCM	68
9	Bn	Et	**3f**	DCM	82

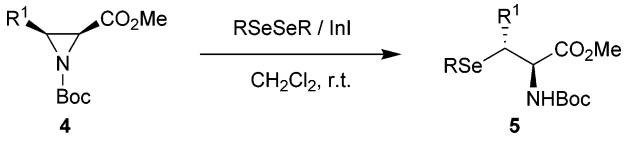
InI and RSeSeR in dichloromethane (Scheme 2).[9a,11] As outlined in the sequence below, the preparation of β-seleno-amines proceeds through the regioselective nucleophilic attack of the organoyl selenide anion at the less hindered position of the aziridine ring.

The reaction was initially conducted with the aziridine **2a** and the phenyl selenolate anion, prepared through the reaction between PhSeSePh and InI in four different solvents (Table 1 entries 1−4). Product **3a** was obtained in dichloromethane with a yield higher than that observed when coordinating solvents were used (compare entries 1−4, Table 1). We attribute that oxygen-donnor solvents and acetonitrile are capable of coordination to the hard metallic center of the indium selenolate **1**, forming stable compexes,[12] competing with the required coordination of the aziridine for the ring-opening reaction. Acetonitrile promotes significative improvement on the reaction yield (entry 3), but the best yield was obtained when the reaction was performed with the noncoordinating solvent dichloromethane (entry 4).

Notably, the indium selenolate **1** promotes faster aziridine ring-opening reaction (4 h) than the selenolate anion generated with $NaBH_4$/EtOH (48 h).[10b] We envisage that this fact is probably due to coordination of the indium(III) complex through the oxygen of the N-Boc group at the initial aziridine (Figure 1). This fact could be supported by the experiment carried out when a trityl group was used as the protecting group of the nitrogen (Table 2, entry 7). In this case no reaction was observed and the starting material could be recovered.

The mild reaction conditions, its speed, and the excellent yields obtained encouraged us to examine the scope and

TABLE 2. Synthesis of Selenocysteine Derivatives



entry	R^1	R	product	time (h)	isolated yield (%)
1	H	Ph	**5a**	6	85
2	H	*p*-ClPh	**5b**	12	98
3	H	*p*-MePh	**5c**	6	60
4	H	*p*-MeOBn	**5d**	24	64
5	Me	Ph	**5e**	28	80
6	Me	*p*-ClPh	**5f**	16	96
7[a]	H	Ph	**5g**	24	

[a] Trityl was used as a protecting group of the nitrogen.

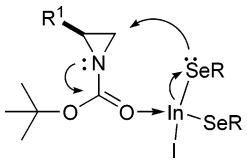


FIGURE 1. Proposed mechanism for the aziridine ring-opening reaction.

generality of the present method. As described in Table 1, all the β-seleno-amines were obtained in good to excellent yields for all the aziridines studied. Concerning the R group, the presence of an electron-donating group, such as methyl, or an electron-withdrawing group, such as chloro, in the aromatic rings of the diselenides has no significant influence on the reactivity of the process, since the products were obtained with a slight decrease in the reaction yield (entries 6 and 7). The reaction was performed also with dialkyl diselenides as the nucleophilic source of selenium, furnishing the products **3e** and **3f** in good yields (entries 8 and 9).

Due to the potential biological activity of selenocysteine and their derivatives, some recent and classical successful approaches aiming at their synthesis have been documented in recent years.[13] In this context, a formidable challenge still remains to develop novel synthetic methods that can permit the introduction of selenium into optically active amino acids, which could be widely explored as building blocks for the synthesis of seleno peptides and derivatives.[14] Thus, we also turned our attention to use this method to synthesize selenocysteine and selenotreonine derivatives, employing the aziridine-2-carboxylate **4** as the starting material (Table 2).

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As we can see in Table 2, a series of selenoamino acids could be synthesized in a straightforward manner allowing some interesting structural diversity. To examine the influence of different electronic properties on the selenolate anions, some substituted aryl diselenides were used, and to our delight, good yields were obtained (Table 2, entries 1−4). Also the reaction could be carried out, with high yields, when aziridines with more steric hindrance at the 3-position were used furnishing the selenotreonine derivatives (Table 2, entries 5 and 6). It is especially noteworthy that all products were obtained without loss of optical purity. This was established by ^{1}H NMR experiments, where single sets of signals for compounds **5e**−**f** were observed and compared to the analytical data obtained for the compounds with the data reported in the literature.[3a,15]

It is worth mentioning that all products have high stability. Besides, some of them are obtained orthogonally protected and can be used directly for the synthesis of a variety of selenopeptides. For example, N-Boc-*Se*-phenylselenocysteine derivatives **5a** (Table 2, entry 1) and the *Se*-*p*-methoxibenzyl-protected amino acid derivatives **5d** (Table 2, entry 4) have been used as precurors for solid-phase peptide synthesis (SPPS) of selenocysteine-containing peptides.[16] Compound **5d** allows the incorporation of free selenocysteine into peptides or the selenocystine derivatives,[17] whereas **5a** is used for the mild oxidative introduction of dehydroalanines.[3c,13c,16]

In summary, the present procedure with indium(I) iodide provides a practical and concise synthesis of a wide range of chiral β-seleno-amines and their derivative in an easy, straightforward, and flexible synthetic route, starting from the easily achieved chiral aziridines.[18] This method offers significant improvements with regards to operational simplicity, reaction time, reaction conditions (room temperature and neutral medium), and high isolated yields of products. More importantly, with the complexes bis(organoylseleno)iodoindium(III), **1**, we could also achieve an efficient and general procedure for the synthesis of selenocysteine and selenotreonine derivatives.

Experimental Section

General Procedure for the Synthesis of Protected Selenocysteines 5. In a 25-mL round-bottomed flask, under an argon atmosphere, InI (powder, 121 mg, 0.5 mmol) was added to a solution of the appropriate diorganyl diselenide (0.5 mmol) in dry CH_2Cl_2 (5 mL). The mixture was allowed to stir until all the InI (15−45 min) was dissolved, then the appropriate protected aziridine (0.5 mmol) was added and the reaction was monitored by TLC. The mixture was quenched with H_2O and extracted with CH_2Cl_2 and the combined organic fractions were collected, dried over $MgSO_4$, and filtered; the solvent was then removed in vacuo yielding the crude products which were purified by flash chromatography on silica gel (9:1 hexane:ethyl acetate).

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Supporting Information Available: Text and figures giving full experimental procedures and characterization data for the compounds discussed in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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