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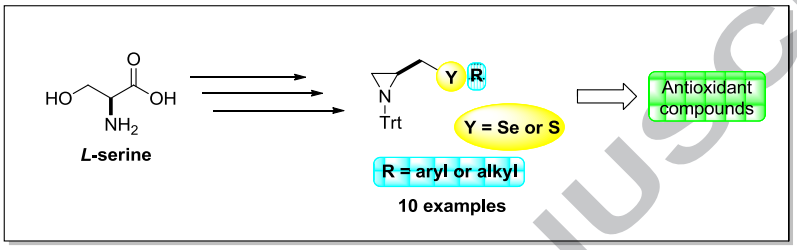

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Straightforward Synthesis and Antioxidant Studies of Chalcogenoaziridines

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ABSTRACT

Herein we reported the synthesis of chalcogenoaziridines through the introduction of the organoselenium moiety in the aziridine framework through the nucleophilic substitution of the OTs leaving group. In addition, the antioxidant activity, as reflected by free radical scavenging, was also evaluated. The new seleno aziridine **6a** showed more effective antioxidant compared to other compounds. These findings also suggest that seleno aziridine **6a** is a promising antioxidant and that its activity is not influenced by the presence of the substituents attached into the aromatic ring.

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1. Introduction

Aziridines are one of the most versatile three-membered ring systems in modern synthetic chemistry. They have been used as precursors of many complex molecules;[1] once they can easily go through a regioselective ring-opening reaction whit nucleophiles.[2] Furthermore, an aziridine moiety can be found in some natural products, and different synthetic compounds of biological interest.[3] In addition, chiral aziridines have been also applied with success as chiral ligands in asymmetric reactions.[4]

In the last decades, there has been a growing interest in developing new methodologies for the preparation of the aziridinyl systems and in this sense, different heteroatom substituents, attached to one or both carbon atoms of the ring have been introduced. Thus, obtaining aziridines, especially optically active aziridines, has become of great importance in organic synthesis.[5]

Moreover, the scope and application of organochalcogen chemistry have increased tremendously, since this class of compounds has continued to attract considerable attention due their biological properties.[6] For instance, it has been demonstrated that organoselenium compounds play an important role as therapeutic compounds, such as antiviral, anticancer agents, and in a variety of situations where free radicals are involved.[7] Furhermore, organochalcogens have been widely studied given their antioxidant activity, which confers neuroprotection, antiulcer, and antidiabetic properties. Among organochalogens, selenium containing molecules may be better nucleophiles,and therefore better antioxidants than classical ones, thus leading to the necessity to design new synthetic organoselenium compounds. In this context, antioxidant pharmacotherapy has emerged as a tool to minimise the biomolecular damage caused by the attack of free radicals. Based on the growing interest in the investigation of the pharmacological and toxicological properties of the organoselenium compounds, several synthetic methods for the preparation of selenoaminoacids, selenium-based peptides, selenium-nucleosides, seleno-carbohydrates and other important natural compounds derivatives are well established, being that an area of intensive research.[8]

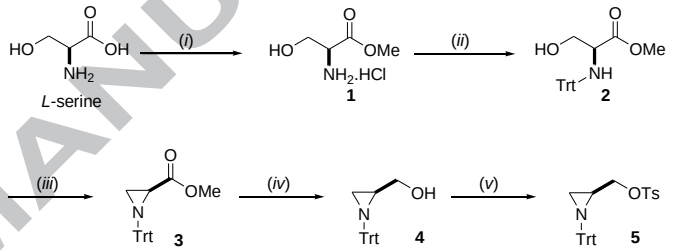
On the other hand, aziridines have been also used as starting materials for the synthesis of β-chalcogen amines which are usually prepared by the regioselective ring opening reaction with chalcogen nucleophiles, generated by different reducing agents. Although β-chalcogen amines represents an important class of compound and were used basically as chiral ligands in different reactions;[9] there are only few examples in the literature reporting the synthesis of chiral chalcogenoaziridines.[10] This fact can be rationalized by locking at the reactivity of the aziridine ring. This ring is suitable to react with a variety of nucleophiles due to its electrophilic nature. In this sense, there is a lack of methodologies for the introduction of nucleophiles on the side chain, maintaining the aziridine ring intact.

Owing to the specific chemical and physical properties of selenium, the incorporation of this group into aziridines compounds can strongly affect the activity of these systems. However, the incorporation of the selenium atom into the side chain of aziridines is much more restricted, and, as far as we know, there are only two papers concerning the preparation of selenoaziridines as sources of aziridinylmethyl radicals.[11]

On account of these aspects and in association with our ongoing research interest toward organochalcogen chemistry,[12] we report herein an efficient and straightforward synthetic route for the preparation of novel chiral chalcogenoaziridines. In addition, the antioxidant activity of these new synthesized compounds was investigated.

2. Results and Discussion

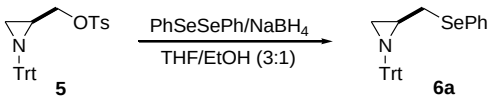
In keeping with our aim, as the starting point of this study, we sought an efficient way to prepare the key chiral tosylate aziridine **5** in a short and high yielding sequence. To accomplish this task, we used some procedures already described in the literature, where the amino acid *L*-serine was first converted into the respectively amino ester **1** by reacting with MeOH in the presence of tionyl chloride. Selective protection of the amino group in **1** as the trityl derivative **2**, followed by the treatment of **2** with methanesulphonyl chloride in THF afforded the aziridine **3** in 76% yield.[13] The *N*-tritylaziridine-2-carboxylic ester **3** was converted into the corresponding *N*-tritylaziridine-2-ylmethanol **4** using lithium aluminium hydride in THF at room temperature for 24 h with 88% yield. The reaction of the primary hydroxyl group with *p*-toluenesulphonyl chloride in the presence of triethylamine and using 4-dimethylaminopydirine as a catalyst delivered the desired tosylate **5** in 87% yield (Scheme1).



Scheme 1. Synthetic strategy to prepare tosylate **5**. Reagents and conditions: (*i*) MeOH, thionyl chloride, overnight, r.t.; (*ii*) trityl chloride, triethylamine, CH_2Cl_2, , 24 h, r.t.; (*iii*) MsCl, triethylamine, THF 0°C, then 48 h, 65°C; (*iv*) $LiAlH_4$, THF, 24 h, r.t.; (*v*) TsCl, triethylamine, DMAP, CH_2Cl_2, 24 h, r.t.

With the required tosylate **5** in hand, we turned our attention to the introduction of the organoselenium moiety in the aziridine framework through the nucleophilic substitution of the OTs leaving group (Table 1). Organoselenium anions were generated through the reaction of diphenyldiselenide with $NaBH_4$ in a mixture of 3:1 THF and ethanol, as previously described.[14] Surprisingly, under these standard conditions, the desired seleno aziridine **6a** was formed in only 51% yield after 24 h (entry 1).

Table 1. Optimization of the reaction conditions for the synthesis of seleno-aziridine **6a**.[a]

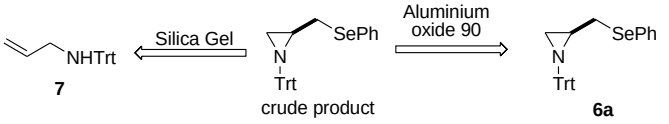


Entry	Time (h)	Temperature (°C)	Yield (%)[b]
1	24	r.t.	51
2	24	66	74
3	12	66	75

[a] All reactions were performed in the presence of tosylate **5** (1.0 mmol), diphenyldisselenide (0.5 mmol) and THF-EtOH (3:1) under nitrogen atmosphere. [b] Isolated yields.

We then tried to conduct the nucleophilic substitution reaction under different conditions, by increasing the temperature. Under reflux, an increase in the yield to 74% was obtained (entry 2). By reducing the reaction time from 24 h to 12 h, no decrease on the reaction yield was observed (entry 3).

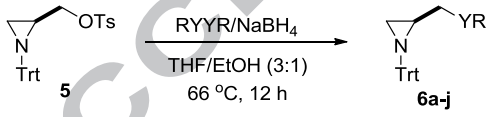
It is worth noting that the purification step is crucial for the achievement of the seleno aziridine in good yields. When the chromatographic column was performed using Silica Gel, the major product isolated after the purification was the allylamine **7** and none of the desired product **6a** was observed.[15] By comparison of the ^{1}H NMR spectra, we could then confirm the absence of signals referent to the alkene in the crude product when compared with the ^{1}H NMR of allylamine **7** (see Supplementary data). Taking this into consideration, we decided to replace Silica Gel by Aluminium Oxide 90 (Standardised for column chromatographic adsorption analysis acc. Brochmann), and to our delight the seleno-aziridine **6a** was isolated in good yield after the purification step (Scheme 2).

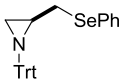
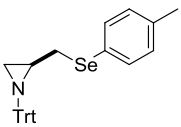
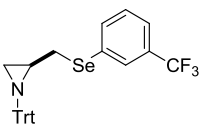
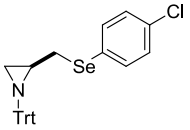
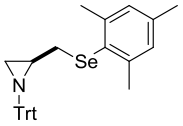
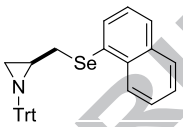
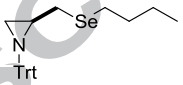
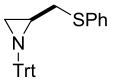
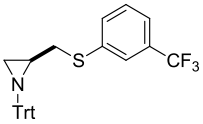
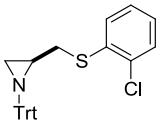


Scheme 2. Chromatographic column performed using Silica Gel and Aluminium oxide 90.

With the optimal condition in hand, we extended the protocol to additional selenium and even sulphur nucleophiles (Table 2 entry 1-10). The reaction was tolerant to a variety of substituents at the aromatic ring of the organoselenium moiety, allowing the preparation of a series of selenoaziridines in moderate and good yields. The reaction was influenced by electronic effects since electron-withdrawing groups such as -chloro, -trifluoromethyl in the aromatic ring afforded better yields (entries 3 and 4) compared with electron-donating groups, -methyl (entry 2). We also employed other diselenide sources in this reaction, e.g. alkyl moiety. For instance, dibuthyl diselenide reacted with tosylate **5**, allowing the preparation of the desired product **6g** in low yield (entry 7). The reaction is also efficient with sulphur nucleophiles, which resulted in the thioaziridines **6h-j** in good yields (entries 8-10).

Table 2. Synthesis of selenium and thioaziridines.[a]



Entry	RYYR	Product		Yield (%)[b]
1	$(PhSe)_2$		**6a**	75
2	$(4\text{-MePhSe})_2$		**6b**	31
3	$(3\text{-}CF_3\text{PhSe})_2$		**6c**	78
4	$(4\text{-ClPhSe})_2$		**6d**	66
5	$(2,4,6\text{-MePhSe})_2$		**6e**	44
6	$(NafSe)_2$		**6f**	46
7	$(BuSe)_2$		**6g**	23
8	$(PhS)_2$		**6h**	49
9	$(3\text{-}CF_3\text{PhS})_2$		**6i**	69
10	$(2\text{-ClPhS})_2$		**6j**	71

[a] All reactions were performed in the presence of tosylate **5** (1.0 mmol), diaryldisselenide (0.5 mmol) and THF-EtOH (3:1) under nitrogen atmosphere. [b] Isolated yields.

3. Effect of Chalcogenoaziridines in Lipid Peroxidation

The effect of chalcogenoaziridines in Lipid Peroxidation assay are given in Table 3. Selenoaziridines **6a**, **6c** and **6d** decreased the levels of lipid peroxidation at concentrations as low as 50 µM, while compounds **6f** and **6g** were effective at concentrations equal or greater than 100 µM. Of these compounds, **6a** was the most potent with the lowest IC_{50} value (70.6 ± 13.65 µM), while **6e** was the least potent (IC_{50} 291.6 ± 202.8 µM). When thioaziridines were evaluated, compound **6h**, was the most efficient with the highest $I_{máx}$ value (68,24 ± 20,30) ,, decreasing the levels of lipid peroxidation at concentrations as low as 10 µM, while compound **6j** (87.5± 45.96) was effective at concentrations equal to or greater than 100 µM. **Aziridine** compound was also tested, showing no ability to reduce lipid peroxidation. This leads us to believe that the addition of selenium and sulfur to the aziridine structure generates an increase in the antioxidant potential of the molecule. The potency of the compounds selenoaziridines, determined by the lowest IC_{50}, follows the order **6a**<**6c**<**6f**<**6d**<**6g**<**6b**<**6e**, and the compounds thioaziridines **6j**≤**6h**<**6i**. The results showed that electronic and steric effects of the substituents attached to the different positions of the phenyl ring had no significant influence on the antioxidant activity.

Table 3. Antioxidant activity of compounds against lipid peroxidation.

Compound	Concentration(μM)					IC_{50} (μM)	I_{max} (%)
	10	50	100	250	500		
6a	97.35 ± 3.57	63.25±5.75**	33.58±12.68***	24.24±17.86***	-	70.6± 13.65	74.76 ± 17.86
6b	99.0 ± 1.73	81.83±28.56	73.42±23.08	-	30.02±9.23*	184.3± 190.1	69.98 ± 9.23
6c	83.18 ± 18.41	56.78±16.53*	41.10±19.84**	29.96±13.68**	-	79.0± 43.28	70.04 ± 13.68
6d	91.17±9.18	60.84±34.10*	48.17±15.67*	29.23±10.57**	-	88.25 ± 20.02	65.65 ± 13.39
6e	87.02±20.4	89.83±20.35	86.29±26.28	-	35.92±34.39*	291.6± 202.8	69.26± 28.43
6f	80.52±9.88	69.33±24.44	38.47±15.68**	24.53±3.43***	-	80.0± 25.0	75.47 ± 3.43
6g	100±0.0	82.94±20.63	53.82±23.63*	-	14.51±8.58***	116.2± 54.06	85.49 ± 8.58
6h	61.64±26.28*	41.59±21.93*	41.38±20.33*	31.76±20.30**	-	89.6± 66.11	68.24 ± 20.30
6i	63.93±18.3	65.79±15.33	61.61±20.91	-	33.25±17.1**	107.5± 15.00	66.75 ± 17.12
6j	69.85±21.2	58.44±26.65	42.26±23.82*	35.31±19.95*	-	87.5± 45.96	67.49 ± 22.79

Data are expressed as mean ± SD (n = 4) of % lipid peroxidation; IC_{50} = concentration (μM) to decrease 50% of lipid peroxidation; I_{max} = % maximal inhibition; * denotes $p< 0.05$; ** $p< 0.01$; *** $p< 0.001$ when compared to control sample by Student-Newman-Keuls test.

4. Effect Effect of Selenoaziridines in FRAP

FRAP assay is a SET (singlet electron transformer) method which is based on the reduction capability of ferric ion (Fe^{3+}) to ferrous ion (Fe^{2+}) of a test sample.[16] Aziridine has the ability to reduce the ferric ion at the concentration of 100 μM (see Table 4). Compound **6a** has the reduce capability at the concentration of 50 μM. The compounds **6b** and **6e** reduced the ferric ion at concentrations of 50-100 μM. The compounds **6d** and **6f** have the potential to reduce concentrations of 10-100 μM. Based in these data, the addition of selenium had the ability to enhance the reducing potential since the aziridine showed reduction of ferric ion at the concentration of 100 uM ($p <0.01$) and the compounds **6d** and **6f** show a reducing potential in concentration of 10 uM ($p <0.01$). All other compounds (Table 3, **6c, 6g, 6h, 6i** and **6j**) did not have an effect in this assay. Thus, the best compounds for reduce ferrous ion are the selenoaziridines **6d** and **6f**. This activity may be due to the high electronegativity of the chlorine attached to the aromatic ring in the compound **6d** and the increase of the size of the aromatic moiety in compound **6f**.

Table 4 - Ferric reducing-antioxidant power (FRAP) assay of compounds

Compound	Concentration (μM)		
	10	50	100
Aziridine	0.106 ± 0.018	0.215 ± 0.011	0.396 ± 0.09**
6a	0.451 ± 0.032	1.43 ± 0.32***	-
6b	0.257 ± 0.06	0.463 ± 0.14*	0.759 ± 0.15***
6d	0.315 ± 0.04**	0.773 ± 0.07***	1.258 ± 0.06***
6e	0.158 ± 0.06	0.819 ± 0.25***	1.144 ± 0.04***
6f	0.288 ± 0.02**	0.772 ± 0.007***	1.315 ± 0.05***

Data are expressed as mean ± SD (n = 3) of absorbance at 593 nm. * $p< 0.05$; ** $p<0.01$; *** $p< 0.001$ when compared with control sample by Student–Newman-Keuls.

5. Conclusions

In summary, we have developed a new and efficient method for the synthesis of chalcogenoaziridines. These compounds were prepared via a concise and flexible route, in good yields, which permitted the preparation of a wide range of compounds with a highly modular character. The use of Aluminium Oxide 90, for the purification of the selenoaziridines, has shown to be crucial in order to obtain the product. Moreover, to the best of our knowledge, this is the first time that the antioxidant activity of chalocogenoaziridines has been reported against a range of free radicals.

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HIGHLIGHTS

- ➔ Synthesis and complete characterization of new chiral chalcogenoaziridines;
- ➔ General method for the synthesis of selenium and sulfur derivatives;
- ➔ Development of a efficient method for the synthesis of functionalized aziridines, without ring opening;
- ➔ Evaluation of the antioxidant activity of the new chiral chalcogenoaziridines;
- ➔ Evaluation of the effect of the chalcogen atom against their antioxidant activity;