Tetrahedron Letters 50 (2009) 2309–2311

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ring opening of unprotected aziridines by zinc selenolates in a biphasic system

Antonio L. Braga [a,b,*], Ricardo S. Schwab [a], Eduardo E. Alberto [a], Syed M. Salman [a], Josimar Vargas [a], Juliano B. Azeredo [b]

[a] Departamento de Química, Universidade Federal de Santa Maria, 97105-900 Santa Maria, RS, Brazil
[b] Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil

ARTICLE INFO

Article history:
Received 27 January 2009
Revised 17 February 2009
Accepted 19 February 2009
Available online 25 February 2009

ABSTRACT

A set of chiral β-seleno amines were prepared by the ring-opening reaction of unprotected aziridines. Under acid conditions diaryl or dialkyl diselenides were reduced by zinc and treated with unprotected aziridines to produce the desired products in good yields. Chiral β-telluro amine was also obtained using this method.

© 2009 Elsevier Ltd. All rights reserved.

In the past decades, selenium-based methods have developed rapidly and become a useful tool in the hands of organic chemists.[1] Organoselenium compounds have found such wide utility because of their effects on an extraordinary number of very different reactions, including many carbon–carbon bond formations, under relatively mild reaction conditions.[2]

Moreover, chiral selenide- and diselenide containing ligands offer attractive and practical options in the development of asymmetric transformations. They have been employed as useful catalysts in enantioselective addition of diethylzinc to aldehydes, conjugate addition of Grignard reagents to enones, and palladium-catalyzed asymmetric allylic substitution.[3] However, the development of new methods for the introduction of selenium-containing groups into organic molecules, particularly in a stereo-controlled manner, remains a significant challenge.[4]

On the other hand, chiral aziridines are one of the most versatile three-membered ring systems in modern synthetic chemistry. They make up a versatile and useful class of nitrogen-containing compounds in organic transformations.[5] They are also key intermediates for the stereo-controlled synthesis of nitrogen containing compounds (e.g., amino acids, heterocycles, and peptides).[6]

In this context, we recently reported the straightforward synthesis of a new set of chiral β-seleno amines through a stereoselective aziridine ring opening with selenium nucleophiles, generated by reducing agents such as $NaBH_4$, $LiBHEt_3$, or indium salts.[7] These compounds were successfully applied as ligands in asymmetric reactions or in the synthesis of selenocysteine derivatives. Despite such progress, it was not possible to promote the ring-opening reaction of unprotected aziridines leading to a tedious and expensive protection–deprotection process.

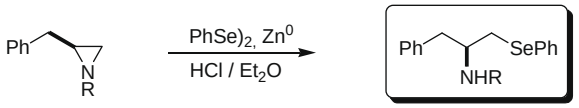
Recently, Santi et al. described a zinc-mediated preparation of selenols and 'in situ' reaction with electrophiles, such as alkyl halides or epoxides.[8] We reasoned that this methodology would be a convenient way to approach the troublesome ring-opening reaction of unprotected aziridines.

Therefore, in connection with our interest in the synthesis and evaluation of [N, Se]-compounds as chiral ligands in asymmetric transformations[9] and in biological screenings,[10] herein we report a simple and efficient synthesis of β-seleno amines. These compounds were easily prepared by reaction of unprotected aziridines and diaryl or dialkyl diselenides. We employed an acid biphasic system and an inexpensive and commercially available zinc dust as reducing agent.

In order to evaluate the performance of the aziridine ring-opening reaction, we firstly used diphenyl diselenide and aziridines derived from L-phenylalanine as standard reagents. Unprotected aziridine **1a**,[11] as well as Ts and Boc-protected aziridines,[12] **1b** and **1c**, respectively, was tested using Zn as reducing agent in an HCl/diethyl ether biphasic system, as illustrated in Scheme 1.

A good result was obtained for unprotected aziridine **1a**, affording the desired β-seleno amine **2a** in 77% yield. The reaction was regioselective, giving the product through the attack of selenolate to the less hindered aziridine carbon. The protected aziridine **1b** (Ts) gave the product in 33% yield, and no product was observed for aziridine **1c** (Boc).

Encouraged by this result, we tested various reaction conditions in an attempt to improve the efficiency of the ring opening of



1a: R = H
1b: R = Ts
1c: R = Boc

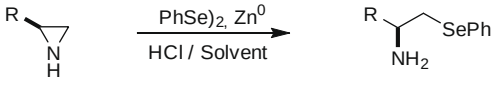
2a: R = H, 77%
2b: R = Ts, 33%
2c: R = Boc, no reaction

Scheme 1. Ring opening of protected and unprotected aziridines **1a–c**.

* Corresponding author. Tel.: +55 55 3220 8761; fax: +55 55 3220 8998.
E-mail address: albraga@quimica.ufsm.br (A.L. Braga).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.156

Table 1
Optimization of the ring-opening reaction of unprotected aziridines by diphenyl diselenide

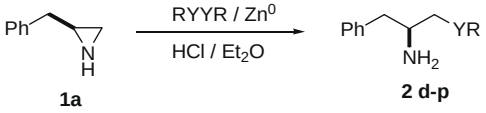


1 2

Entry[a]	R	Solvent	Temp (°C)	Yield[b] (%)
1	Bn	Et_2O	rt	77
2	Bn	THF	rt	64
3	Bn	Hexane	rt	26
4	Bn	AcOEt	rt	75
5	Bn	CH_2Cl_2	rt	60
6	Bn	EtOH	rt	52
7	Bn	H_2O	rt	53
8	Bn	Et_2O	Reflux	60
9	Bn	AcOEt	Reflux	43
10	*i*-Pr	Et_2O	rt	58
11	*i*-Bu	Et_2O	rt	70

[a] Reagents and conditions: Et_2O (4 mL), HCl (10%, 4 mL), PhSeSePh (0.25 mmol), and zinc dust (7.7 mmol). 10–30 min after addition of unprotected aziridine (0.5 mmol).
[b] Isolated yields.

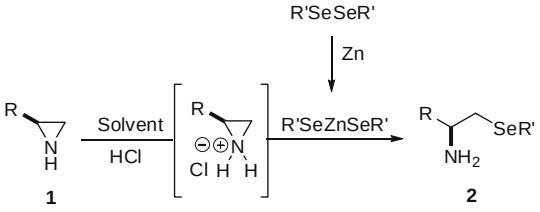
Table 2



1a 2 d-p

Entry	R	Y	Product	Yield[a] (%)
1	2-MeC_6H_4	Se	**2d**	35
2	4-MeC_6H_4	Se	**2e**	60
3	2-ClC_6H_4	Se	**2f**	55
4	4-ClC_6H_4	Se	**2g**	80
5	4-FC_6H_4	Se	**2h**	83
6	2-$OMeC_6H_4$	Se	**2i**	51
7	4-$OMeC_6H_4$	Se	**2j**	58
8	2-Pyridyl	Se	**2k**	46
9	Bn	Se	**2l**	35
10	*n*-Bu	Se	**2m**	35
11	Et	Se	**2n**	52
12	Ph	Te	**2o**	40

[a] Isolated yields.



1 2

Scheme 2. Proposed mechanism for zinc-mediated ring opening of unprotected aziridines by diselenides.

unprotected aziridines (Table 1). We chose PhSeSePh as standard diselenide, and to check the best solvent and temperature for this system we selected aziridine **1a** as substrate (entries 1–9).

The complete conversion of diselenide into the corresponding selenolate by the addition of zinc under acid conditions was demonstrated by discoloration of the mixture which was followed by the addition of aziridine. It was found that the solvent had a strong influence on the formation of the product, while ethereal solvents such as Et_2O and THF, showed better results (entries 1 and 2). Apolar hexane (entry 3) did not afford the β-seleno amine **2** in an appreciable yield. The use of CH_2Cl_2 allowed the formation of product **2** in 60% yield (entry 5). A good result was also achieved by using ethyl acetate, giving the product in a yield close to that achieved with Et_2O (entry 4). In an attempt to make the reaction more environmentally friendly, we employed solvents such EtOH and water (entries 6 and 7), but unfortunately the product was obtained only in moderate yield. In addition, the reaction was carried out in Et_2O and AcOEt under reflux in an effort to increase the yield, but quite disappointing results were observed (entries 8 and 9). When the reaction was performed with aziridines derived from L-valine and L-leucine (entries 10 and 11) using the best conditions, the products were obtained in good yields, but slightly lower than those found for aziridine **1a** derived from L-phenylalanine.

Based on these results and in order to widen the scope of our protocol, we then tested a broader range of diselenides.[13] The results are listed in Table 2. Notably, electron-withdrawing groups showed better results compared to electron-donating ones. In the reaction using 4-$ClC_6H_4Se)_2$ and 4-$FC_6H_4Se)_2$ the yields were 80% and 83%, respectively (entries 4 and 5), which were quite higher than the results for 4-$MeC_6H_4Se)_2$ and 4-$MeOC_6H_4Se)_2$ (60% and 58%; entries 2 and 7). Another feature of this system is the strong influence of hindrance effects in the diselenide moiety. When *ortho*-substituted diselenides were applied, there was a dramatic decrease in yields both for electron-donating and -withdrawing groups (entries 1, 3, and 6 vs 2, 4, and 7). Dibenzyl diselenide and 2-pyridine diselenide were also tested (entries 8 and 9). The β-seleno amines **2m** and **2n**, with aliphatic moieties attached to selenium were also obtained by using dibutyl diselenide and diethyl diselenide (entries 10 and 11). To further improve our method, we promoted the reaction using diphenyl ditelluride. Although the yield was 40% (entry 12) our approach is a promising strategy for the preparation of β-telluro amine, which is a current goal in organochalcogen chemistry, due to difficulties in its preparation and handling.[9g,h]

We believe that the reaction occurs firstly through the 'in situ' formation of water-soluble zinc selenolate. The activation of the unprotected aziridine leads to the protonated intermediate, which undergoes the ring opening by zinc selenolate in the aqueous layer, as depicted in Scheme 2. We conjecture that the protonation of the aziridines is the most crucial step, activating them to undergo the ring-opening reaction by zinc selenolates. An important feature of the present method is its regioselectivity, as the product is given exclusively through the attack of selenolate to the less-hindered aziridine carbon. Moreover, HPLC analysis of the β-seleno amines **2** and authentic samples showed the retention of the configuration of the chiral center, demonstrating that there was no racemization of the incoming product.[7a]

In summary, we presented in this report a simple and efficient approach for the preparation of chiral β-seleno amines. The desired products were prepared in a biphasic system, employing inexpensive and commercially available zinc dust, unprotected aziridines, and alkyl or aryl diselenides. A notable feature of our approach is the regioselectivity of the ring-opening reactions of unprotected aziridines, leading to the desired products in good yields, which avoids expensive protection-deprotection chemistry. A broad set of chiral β-seleno amines was synthesized, as well as a β-telluride amine analogue.

Acknowledgments

The authors thank CNPq, Capes, INCT-Catálise, and FAPERGS for financial support. S.M.S. thanks TWAS-CNPq for the PhD fellowship.

References and notes

1. (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697; (b) Nicolaou, K. C.; Petasis, N. A. Selenium in Natural Products Synthesis; CIS: Philadelphia, PA, 1984; (c) Liotta, D. Organoselenium Chemistry; Wiley: New York, 1987; (d) Back, T. G. Organoselenium Chemistry: A Practical Approach; Oxford University Press: Oxford, UK, 1999; (e) Wirth, T.. *Organoselenium Chemistry—Modern Developments in Organic Synthesis*. In *Topics in Current Chemistry*; Springer: Heidelberg, Germany, 2000; Vol. 208.
2. (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154; (b) Seebach, D.; Peleties, N. *Chem. Ber.* **1972**, *105*, 511; (c) Seebach, D.; Beck, A. K. *Angew. Chem., Int. Ed.* **1974**, *13*, 806; (d) Reich, H. J. *J. Org. Chem.* **1975**, *40*, 2570; (e) Reich, H. J.; Shah, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 3250; (f) Sevrin, M.; Vanende, D.; Krief, A. *Tetrahedron Lett.* **1976**, *30*, 2643; (g) Sevrin, M.; Dumont, W.; Hevesi, L. D.; Krief, A. *Tetrahedron Lett.* **1976**, *30*, 2647; (h) Braga, A. L.; Reckziegel, A.; Silveira, C. C.; Comasseto, J. V. *Synth. Commun.* **1994**, *24*, 1165; (i) Braga, A. L.; Zeni, G.; Andrade, L. H.; Silveira, C. C. *Synlett* **1997**, 595; (j) Braga, A. L.; Zeni, G.; Andrade, L. H.; Silveira, C. C.; Stefani, H. A. *Synthesis* **1998**, 39; (k) Silveira, C. C.; Braga, A. L.; Vieira, A. S.; Zeni, G. *J. Org. Chem.* **2003**, *68*, 662; (l) Mlochowski, J.; Brzaszcz, M.; Giurg, M.; Palus, J.; Wójtowicz, H. *Eur. J. Org. Chem.* **2003**, 4329; (m) Detty, M. R.; Goodman, M. A. *Synlett* **2006**, 1100.
3. For a comprehensive review about the use of chiral organoselenium in asymmetric catalisys see: (a) Wirth, T. *Tetrahedron* **1999**, *55*, 1; (b) Wirth, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3741; (c) Braga, A. L.; Lüdtke, D. S.; Vargas, F.; Braga, R. C. *Synlett* **2006**, 1453; (d) Braga, A. L.; Lüdtke, D. S.; Vargas, F. *Curr. Org. Chem.* **2006**, *10*, 1921.
4. (a) Mukherjee, C.; Tiwari, P.; Misra, A. K. *Tetrahedron Lett.* **2006**, *47*, 441; (b) Tiwari, P.; Misra, A. K. *Tetrahedron Lett.* **2006**, *47*, 2345; (c) Caputo, R.; Capone, S.; Greca, M. D.; Longobardo, L.; Pinto, G. *Tetrahedron Lett.* **2007**, *48*, 1425; (d) Abdo, M.; Knapp, S. *J. Am. Chem. Soc.* **2008**, *130*, 9234; (e) Andrade, L. H.; Silva, A. V. *Tetrahedron: Asymmetry* **2008**, *19*, 1175; (f) Rafinski, Z.; Scianowski, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1237.
5. *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006.
6. (a) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Aziridines and Azirines Monocyclic*; Padwa, A., Ed.; Comprehensive Heterocyclic Chemistry II; Pergamon Press: Oxford, 1996; Vol. 1A, pp 1–60; For a comprehensive review about aziridine ring opening see: (b) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701; (c) Braga, A. L.; Lüdtke, D. S.; Paixão, M. W.; Alberto, E. E.; Stefani, H. A.; Juliano, L. *Eur. J. Org. Chem.* **2005**, *20*, 4260.
7. (a) Braga, A. L.; Lüdtke, D. S.; Paixão, M. W.; Rodrigues, O. E. D. *Org. Lett.* **2003**, *5*, 2635; (b) Braga, A. L.; Paixão, M. W.; Marin, G. *Synlett* **2005**, 1675; (c) Braga, A. L.; Schneider, P. H.; Paixão, M. W.; Deobald, A. M.; Peppe, C.; Bottega, D. P. *J. Org. Chem.* **2006**, *71*, 4305.
8. Santi, C.; Santoro, S.; Testaferri, L.; Tiecco, M. *Synlett* **2008**, 1471.
9. For selected examples see: (a) Braga, A. L.; Silva, S. J. N.; Lüdtke, D. S.; Drekener, R. L.; Silveira, C. C.; Rocha, J. B. T.; Wessjohann, L. A. *Tetrahedron Lett.* **2002**, *43*, 7329; (b) Braga, A. L.; Milani, P.; Paixão, M. W.; Zeni, G.; Rodrigues, O. E. D.; Alves, E. F. *Chem. Commun.* **2004**, 2488; (c) Schneider, P. H.; Schrekker, H. S.; Silveira, C. C.; Wessjohann, L. A.; Braga, A. L. *Eur. J. Org. Chem.* **2004**, 2715; (d) Braga, A. L.; Paixão, M. W.; Milani, P.; Silveira, C. C.; Rodrigues, O. E. D.; Alves, E. F. *Synlett* **2004**, 1297; (e) Braga, A. L.; Lüdtke, D. S.; Vargas, F.; Paixão, M. W. *Chem. Commun.* **2005**, 2512; (f) Braga, A. L.; Lüdtke, D. S.; Alberto, E. E.; Sehnem, J. A. *Tetrahedron* **2005**, *61*, 11664; (g) Braga, A. L.; Sehnem, J. A.; Vargas, F.; Braga, R. C. *J. Org. Chem.* **2005**, *70*, 9021; (h) Braga, A. L.; Vargas, F.; Galetto, F. Z.; Paixão, M. W.; Schwab, R. S.; Taube, P. T. *Eur. J. Org. Chem.* **2007**, 5327; (i) Schwab, R. S.; Galetto, F. Z.; Azeredo, J. B.; Braga, A. L.; Lüdtke, D. S.; Paixão, M. W. *Tetrahedron Lett.* **2008**, *49*, 5094.
10. Selected examples: (a) Farina, M.; Barbosa, N. B. V.; Nogueira, C. W.; Folmer, V.; Zeni, G.; Andrade, L. H.; Braga, A. L.; Rocha, J. B. T. *Braz. J. Med. Biol. Res.* **2002**, *35*, 636; (b) Burger, M.; Fachinetto, R.; Calegari, L.; Paixão, M. W.; Braga, A. L.; Rocha, J. B. T. *Brain Res. Bull.* **2004**, *64*, 339; (c) Rosa, R. M.; de Oliveira, R. B.; Saffi, J.; Braga, A. L.; Roesler, R.; Pizzol, F. D.; Moreira, J. C. F.; Brendel, M.; Henriques, J. A. P. *Life Sci.* **2005**, *77*, 2398; (d) Centurião, F. B.; Corte, C. L. D.; Paixão, M. W.; Braga, A. L.; Zeni, G.; Emanuelli, T.; Rocha, J. B. T. *Brain Res.* **2005**, *1039*, 146; (e) Soares, F. A.; Farina, M.; Böettcher, A. C.; Braga, A. L.; Rocha, J. B. T. *Environ. Res.* **2005**, *98*, 46; (f) de Avila, D. S.; Beque, M. C.; Folmer, V.; Braga, A. L.; Zeni, G.; Nogueira, C. W.; Soares, F. A. A.; Rocha, J. B. T. *Toxicology* **2006**, *224*, 100; (g) Braga, A. L.; Alberto, E. E.; Soares, L. C.; Rocha, J. B. T.; Sudati, J. H.; Ross, D. H. *Org. Biomol. Chem.* **2009**, *7*, 43.
11. Kashelikar, D. V.; Fanta, P. E. *J. Am. Chem. Soc.* **1960**, *82*, 4930.
12. (a) Rai, K. M. L.; Hassner, A. *Adv. Strain. Interest. Org. Mol.* **2000**, *8*, 187; (b) Mitsunobu, O. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon: Oxford, 1990; (c) Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Lwowski, L., Eds.; Pergamon: Oxford, 1991; (d) Murphree, S. S.; Padwa, A. *Prog. Heterocycl. Chem.* **2001**, *13*, 52.
13. *General procedure*: In a 25 mL round-bottomed flask, under argon atmosphere, was prepared the biphasic solution by the addition of Et_2O (4 mL) and HCl (10%, 4 mL), to this solution were added firstly the diaryl or dialkyl diselenide (0.25 mmol) and zinc dust (500 mg, 7.7 mmol). The mixture was allowed to stir until the yellow solution became colourless (10–30 min), then the unprotected aziridine (0.5 mmol) was added and the reaction was stirred at room temperature for 24 h. After completion of the reaction, as indicated by TLC, the reaction mixture was treated with saturated aqueous ammonium chloride solution and the whole mixture was extracted 3 times with CH_2Cl_2 and the combined organic fractions were collected, dried over $MgSO_4$, filtered and the solvent was then removed in vacuo. The crude mixture was purified by column chromatography on silica gel eluting with hexane–ethyl acetate (9:1) and after with ethyl acetate.