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Regioselective ring-opening of aziridines with diselenides and disulfides using the Zn/$AlCl_3$ system

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Regioselective ring-opening of aziridines with diselenides and disulfides using the $Zn/AlCl_3$ system

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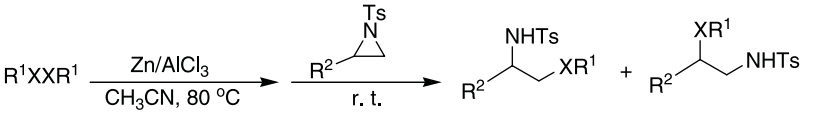
An efficient $Zn/AlCl_3$-promoted highly regioselective one-pot procedure has been demonstrated for the synthesis of β-amino selenides and sulfides from a variety of diselenides/disulfides and aziridines by reductive cleavage of Se–Se and S–S bonds using the $Zn/AlCl_3$ system in acetonitrile under very mild conditions.



Keywords: β-amino selenides; β-amino sulfides; diselenides; disulfides; $Zn/AlCl_3$ system

1. Introduction

The impact of organosulfur and organoselenium chemistry on modern organic synthesis is undisputable and has played enormous roles in biology and medicine (*1*). Among them, β-amino sulfides and selenides are the key building blocks for the synthesis of many bioactive molecules (*2*). Examples are thiol proteins and selenocysteine (Se-Cys). Thiol proteins are important in cellular antioxidant defenses and redox signaling (*3*); selenocysteine, recognized as the 21st amino acid in ribosome-mediated protein synthesis, has both a lower pK_a and a higher reduction potential than cysteine itself, which make it very suitable in proteins that are involved in the antioxidant activity (*4*). Furthermore, a wide range of organoselenium and organosulfur compounds are now accepted as useful antibiotics, anticancer, antimicrobial, anti-inflammatory and antiviral agents (*5*).

The most straightforward method for the preparation of β-amino sulfides involves the regioselective ring-opening reaction of aziridines with thiols using base as catalyst (*6*) or Lewis acids such as $Bi(OTf)_3$, $LiClO_4$, $ZnCl_2$ and $BF_3.OEt_2$ or Bronsted acids such as CF_3SO_3H have been employed (*7*).

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Among the useful and general methods for the preparation of β-amino sulfides, we can cite those involving the reaction of olefins with benzeneselenenyl chloride and amines (*8*), addition of benzene selenol to aziridines in the presence of triethylamine (*9*) and nucleophilic ring-opening of aziridine derivatives by attack of either RSeSeR/$NaBH_4$ (*10*) or PhSeSePh/$(n\text{-Bu})_3P$ (*11*). Recently, Ganesh and Chandresekaran (*12*) introduced an efficient procedure for the synthesis of β-amino selenides and sulfides by aziridine ring-opening with selenolate and thiolate anions derived from diselenides/disulfides in the presence of Rongalite (sodium hydroxymethanesulfinate). In another recent report, β-amino selenides were prepared by the ring-opening of unprotected aziridines using the RSeSeR/Zn/HCl/Et_2O biphasic system under an argon atmosphere; however, the yields were moderate (35–83%) for unprotected aziridines and low (33%) for protected (*N*-tosyl)aziridine (*13*).

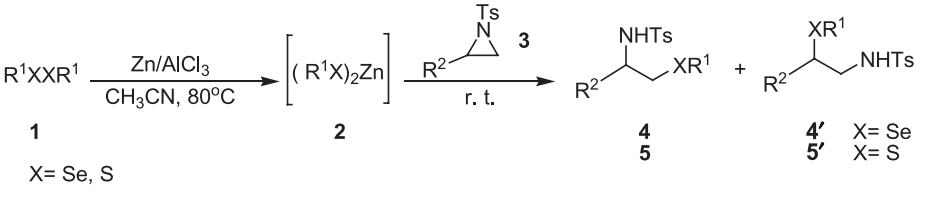
2. Results and discussion

In continuation of our previous work on the synthetic utility of zinc selenolates and thiolates (*14*), we now disclose that zinc selenolate/thiolate, prepared *in situ* via the reductive cleavage of diselenide/disulfide in the presence of Zn/$AlCl_3$, is an effective reagent for the nucleophilic ring-opening of aziridines in a regioselective manner at room temperature under an ambient atmosphere (Scheme 1).

Simple stirring of diselenides/disulfides **1** with metallic zinc dust in the presence of aluminum(III) chloride in dry acetonitrile at 80 °C produced the zinc thiolate/selenolate **2**. Then, the mixture was cooled to room temperature followed by addition of *N*-tosylaziridines **3**, which gave, after workup, the desired products **4**/**4′** and **5**/**5′** in high to excellent yields (*15*). The presence of aluminum chloride is essential, and in the absence of this Lewis acid, the reaction does not proceed at all.

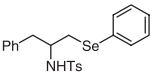
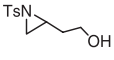
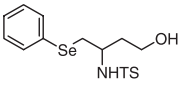
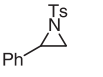
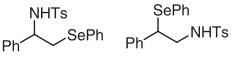
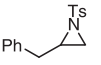
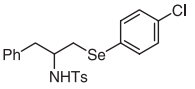
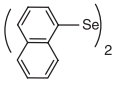
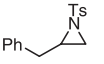
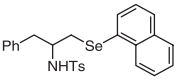
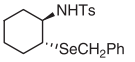
Various diselenides were chosen to investigate the ring-opening of different *N*-tosylaziridines. The results are summarized in Table 1. In contrast to two recent reports in which dialkyl diselenides gave a low yield (*13*) of the ring-opened product, or no product at all even after 24 h (*12*), our method gave a high yield (80%) of the corresponding β-amino selenide **4g** from the reaction of aziridine **3a** with dibenzyl diselenide (Entry 7, Table 1). As can be seen from Table 1, in the case of unsymmetrical aziridines, the reaction proceeds with regioselectivity because in all cases selenolate anions exclusively attack the less hindered carbon of the aziridine to give the single regioisomer **4** (Scheme 1). The only exception is given by styrene-derived aziridine **3d** (Entry 4, Table 1), where a large proportion (83%) of the other regioisomer (**4′d**) was detected. This is due to the partial stabilization of developing a positive charge at the more hindered site of the aziridine.

The versatility of the reaction was explored further by extending the methodology to cleave the disulfide bond and its utility to the synthesis of β-amino sulfides. As in the case of diselenides, disulfides can also undergo a reductive cleavage in the presence of the Zn/$AlCl_3$ system. Several *N*-tosylaziridines were converted to β-amino sulfides **5**/**5′** in high to excellent yields by the reaction of zinc thiolates in acetonitrile at room temperature. The results are tabulated in Table 2. The



Scheme 1. Zn/$AlCl_3$-promoted synthesis of β-amino selenides and sulfides.

Table 1. Synthesis of β-amino selenides from diselenides and various aziridines in the presence of $Zn/AlCl_3$ system.

Entry	$R^1Se–SeR^1$	Aziridine	Product	Yield (%)[a,b]
1	$(PhSe)_2$	 **3a**	 **4a**	90 (*12*)
2	$(PhSe)_2$	 **3b**	 **4b**	89 (*12*)
3	$(PhSe)_2$	 **3c**	 **4c**	87 (*12*)
4	$(PhSe)_2$	 **3d**	 **4d** **4′d**	90 (*12*) (17:83)[c]
5	$(4\text{-}ClC_6H_4Se)_2$	 **3b**	 **4e**	86 (*12*)
6		 **3b**	 **4f**	91 (*12*)
7	$(PhCH_2Se)_2$	 **3a**	 **4g**	80 (15)

Notes: [a]Isolated yields. [b]References are provided for known compounds. [c]Based on the ^1H NMR data.

unsymmetrical aziridines **3b** and **3c** underwent ring-opening, exclusively from the less hindered carbon, while the styrene-derived aziridine **3d** gave the opposite regioselectivity in comparison with 2-alkyl aziridines (Entries 4 and 9, Table 2).

3. Conclusion

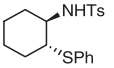
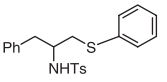
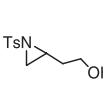
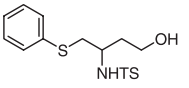
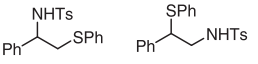
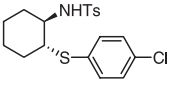
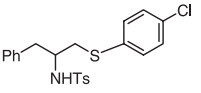
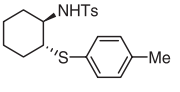
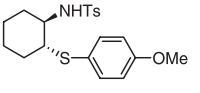
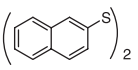
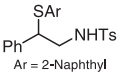
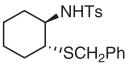
In conclusion, the new procedure described here appears to be highly competitive with other methods reported in the literature, and in some cases better results are obtained, especially in terms of reaction time and yields (*7a, 11, 13*). It has been shown that the methods reported here are very efficient for the ring-opening of aziridines, with high regioselectivity, under simple and relatively mild conditions.

4. Experimental

4.1. *General procedure*

A mixture of diselenide/disulfide (0.5 mmol), activated Zn dust (2.5 mmol) and anhydrous $AlCl_3$ (1.0 mmol) was suspended in anhydrous MeCN (5 mL). The mixture was refluxed, with stirring for 1.5–2 h, during which time the zinc powder was almost consumed. Then, the mixture was cooled

Table 2. Reaction of aziridines with disulfides in the presence of the $Zn/AlCl_3$ system.

Entry	$R^1S–SR^1$	Aziridine		Product		Yield (%)[a,b]
1	$(PhS)_2$		**3a**		**5a**	91 (*12*)
2	$(PhS)_2$		**3b**		**5b**	91 (*12*)
3	$(PhS)_2$		**3c**		**5c**	88 (*12*)
4	$(PhS)_2$		**3d**		**5d** **5′d**	93 (*12*) (29:71)[c]
5	$(4\text{-}ClC_6H_4S)_2$		**3a**		**5e**	87 (*16*)
6	$(4\text{-}ClC_6H_4S)_2$		**3b**		**5f**	89 (*12*)
7	$(4\text{-}MeC_6H_4S)_2$		**3a**		**5g**	86 (*17*)
8	$(4\text{-}MeOC_6H_4S)_2$		**3a**		**5h**	85 (*16*)
9			**3d**		**5′i**	90 (*16*)
10	$(PhCH_2S)_2$		**3a**		**5j**	78 (*15*)

Notes: [a]Isolated yields. [b]References are given for known compounds. [c]Based on the ^{1}H-NMR integration values.

to room temperature, the aziridine (1.0 mmol) was added in one portion and stirring was continued for 1 h at room temperature followed by evporation of the organic solvent. Water (10 mL) was added to the residue; the organic layer was extracted with CH_2Cl_2 (2×10 mL), dried (Na_2SO_4) and evaporated. Preparative TLC (silica gel, *n*-hexane-EtOAc) yielded the pure products.

5. Selected physical and spectral data

5.1. *2-(Phenylselanyl)-N-tosylcyclohexanamine (Table 1, 4a)*

White crystals; m.p. 134–135 °C; IR (KBr): 3271 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15–1.34 (m, 4H), 1.53–1.71 (m, 2H), 2.04–2.08 (m, 1H), 2.22–2.34 (m, 1H), 2.43 (s, 3H), 2.97–3.03

(m, 2H), 5.18 (br d, $J = 4.0$ Hz, 1H), 7.20–7.38 (m, 7H), 7.75 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.5, 23.3, 25.2, 28.3, 32.2, 47.6, 55.8, 128.8, 129.4, 130.6, 130.9, 131.8, 135.4, 138.6.

5.2. *2-Phenyl-2-(phenylselanyl)-N-tosylethanamine (Table 1, 4′d)*

Light yellow oil; IR (neat): 3281 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.34–3.40 (m, 2H), 4.14 (t, $J = 7.4$ Hz, 1H), 4.77 (br t, $J = 5.9$ Hz, 1H), 7.12–7.14 (m, 2H), 7.20–7.32 (m, 10H), 7.64 (d, $J = 8.3$ Hz, 2H).

5.3. *1-(4-Chlorophenylselanyl)-3-phenyl-N-tosylpropan-2-amine (Table 1, 4e)*

Colorless crystals; m.p. 58–60 °C; IR (KBr): 3287 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.60–2.84 (m, 2H), 2.91 (dd, $J = 13.5$, 6.0 Hz, 1H), 3.08 (t, $J = 7.4$ Hz, 1H), 3.29–3.48 (m, 1H), 4.85 (d, $J = 7.0$ Hz, 1H), 6.87–6.89 (m, 2H), 6.97–7.18 (m, 7H), 7.27 (d, $J = 8.3$ Hz, 2H), 7.38 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 32.9, 39.7, 54.0, 125.9, 126.3, 126.8, 127.9, 128.2, 128.8, 129.1, 129.2, 133.8, 135.9, 136.1, 142.9.

5.4. *1-(1-Naphthylselanyl)-3-phenyl-N-tosylpropan-2-amine (Table 1, 4f)*

Light yellow oil; IR (neat): 3274 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.73–2.80 (m, 2H), 2.95 (dd, $J = 13.4$, 6.3 Hz, 1H), 3.17 (dd, $J = 12.5$, 4.7 Hz, 1H), 3.39–3.48 (m, 1H), 4.72 (d, $J = 7.0$ Hz, 1H), 6.85 (d, $J = 8.2$ Hz, 4H), 7.08–7.13 (m, 3H), 7.30 (m, 2H), 7.33 (t, $J = 8.0$ Hz, 1H), 7.48–7.52 (m, 2H), 7.66 (d, $J = 6.1$ Hz, 1H), 7.79–7.85 (m, 2H), 8.21–8.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.0, 32.4, 39.9, 54.1, 125.5, 125.9, 126.4, 126.5, 126.7, 127.0, 128.1, 128.4, 128.6, 128.9, 129.0, 129.2, 130.1, 132.5, 133.8, 136.2, 136.3, 142.4.

5.5. *2-(Phenylthio)-N-tosylcyclohexanamine (Table 2, 5a)*

White crystals; m.p. 130–131 °C; IR (KBr): 3276 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19–1.43 (m, 4H), 1.52–1.60 (m, 2H), 1.96–2.08 (m, 1H), 2.12–2.23 (m, 1H), 2.42 (s, 3H), 2.91–3.04 (m, 2H), 5.46 (d, $J = 4.4$ Hz, 1H), 7.20–7.37 (m, 7H), 7.75 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 23.2, 24.4, 31.5, 32.1, 51.2, 55.2, 127.3, 127.6, 128.9, 129.6, 132.9, 137.3, 143.3.

5.6. *2-Phenyl-2-(phenylthio)-N-tosylethanamine (Table 2, 5′d)*

Light yellow oil; IR (neat): 3291 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.38 (t, $J = 7.4$ Hz, 1H), 4.15 (t, $J = 7.6$ Hz, 1H), 4.81–4.92 (m, 1H), 5.03 (br t, $J = 6.5$ Hz, 1H), 7.10–7.33 (m, 12H), 7.64 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 47.1, 52.5, 127.0, 127.1, 127.8, 127.9, 128.9, 129.0, 129.8, 132.6, 136.8, 138.2, 143.5.

5.7. *2-(4-Methoxyphenylthio)-N-tosylcyclohexanamine (Table 2, 5h)*

White crystals; m.p. 102–103 °C; IR (KBr): 3276 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15–1.30 (m, 4H), 1.51–1.56 (m, 2H), 1.88–2.00 (m, 1H), 2.07–2.24 (m, 1H), 2.40 (s, 3H), 2.64–2.76 (m, 1H), 2.86–2.97 (m, 1H), 3.76 (s, 3H), 5.61 (d, $J = 4.4$ Hz, 1H), 6.74 (d, $J = 8.6$ Hz, 2H), 7.19 (d, $J = 8.6$ Hz, 2H), 7.26 (d, $J = 8.1$ Hz, 2H), 7.75 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 21.5, 23.4, 24.6, 31.5, 32.2, 52.0, 55.1, 55.3, 114.4, 122.5, 127.3, 129.6, 136.3, 137.5, 143.3, 159.8.

5.8. *2-(Naphthalen-2-ylthio)-2-phenyl-N-tosylethanamine (Table 2, 5′i)*

Colorless crystals; m.p. 135–136 °C; IR (KBr): 3290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.20–3.35 (m, 2H), 4.21 (t, $J = 7.3$ Hz, 1H), 4.62 (br s, 1H), 7.14–7.30 (m, 8H), 7.37–7.55 (m, 4H), 7.56–7.80 (m, 4H);^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 47.3, 52.7, 126.1, 126.3, 126.6, 127.3, 127.7, 127.9, 128.2, 128.7, 128.8, 129.4, 130.3, 131.0, 132.4, 133.5, 137.4, 138.6, 143.0.

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