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Stereospecific synthesis of 2,3-disubstituted aziridines from β-alkylamino phenylselenides

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Abstract

Reduction of α-phenylselanyl imines derived from β-phenylselanyl α-oxoesters or PhSeCl assisted nucleophilic addition of primary amines to α,β-unsaturated esters have led to β-alkylamino phenylselenides **4**, **5**, **12** and **13** which were cyclised into aziridines **8**, **9** and **14** after selenium activation. *threo*-Amino selenides led stereospecifically to *cis*-2,3-disubstituted aziridines. Depending on the structure, non-functionalised amino selenides **19**–**20** were also cyclised into aziridines **21**–**22**.

The aziridine nucleus is included in some natural substances which present antitumour and antibiotic activity. Synthetic chiral aziridines have also shown biological properties and are pivotal targets for the synthesis of chiral functionalised compounds. Efficient methods have been proposed for the stereocontrolled preparation of mono, di and trisubstituted optically active aziridines. Two recent reviews report on the synthetic routes and on the principal reactions in relation with stereoselective ring opening processes.[1,2]

A convenient and efficient aziridine synthesis is based on the S_N2 cyclisation of amino alcohols after derivation of the hydroxy group. Enantiomerically pure starting materials are: amino acids, carbohydrates, and hydroxy acids. Catalysed asymmetric reactions of alkenes with nitrenoid compounds or imines with carbenes have been proposed. The synthesis of optically active aziridines via an internal S_N2 displacement of a sulfonium group has been also studied. Sulfonamides and carbamates are used as nucleophilic nitrogen groups and activated aziridines were obtained after basic treatment.[3–5]

The formation of epoxides from β-hydroxy selenides through internal S_N2 displacement of a methyl selenonium group is well known.[6–8] The *cis* or *trans* stereochemistry of 2,3-disubstituted epoxides allows the determination of the *threo* or *erythro* nature of the substrates. The absolute configuration of 3-phenylselanyl 1,2-diol derivatives was assigned by this way.[9]

We describe here the first synthesis of aziridines from β-alkylamino selenides.The reduction of the unstable imines **2** (R^3=benzyl), derived from β-phenylselanyl α-oxoesters **1**,[10] gave the amino selenides **4**. The ester group controls the stereochemistry of the reaction and one diastereoisomer was formed

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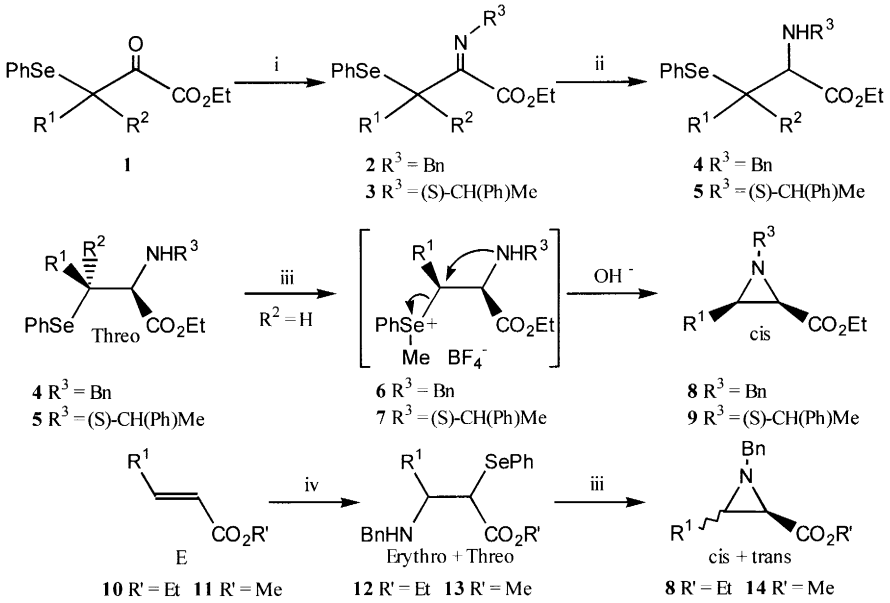


Scheme 1. (i) R^3NH_2 (4 equiv.), $TiCl_4$ (0.66 equiv.), Et_2O, rt, 5 h. (ii) $NaBH_3CN$ (1.5 equiv.), AcOH (1 equiv.), EtOH, 0°C, 1 h. (iii) $Me_3O^+BF_4^-$ (2 equiv.), CH_2Cl_2, rt, then 1N NaOH aq. solution. (iv) PhSeCl (1.2 equiv.), $ZnCl_2$ (0.3 equiv.), CH_2Cl_2, rt, 0.5 h, then $BnNH_2$ (2.5 equiv.), rt, 14 h

Table 1
Amino selenides **4**, **5**, **12** and **13** and aziridines **8**, **9** and **14**

Entry	Substrate			Amino selenide			Aziridine		
	N°	R^1	R^2	N°	Yield (%)	Erythro/Threo	N°	Yield (%)	Trans/Cis[a]
1	**1a**	Me	H	**4a**	47	0 / 100	**8a**	49	0 / 100
2	**1b**	Et	"	**4b**	54	0 / 100	**8b**	57	0 / 100
3	**1c**	nPr	"	**4c**	51	0 / 100	**8c**	61	0 / 100
4	**1d**	Bn	"	**4d**	52	0 / 100	**8d**	48	0 / 100
5	**1e**	iPr	"	**4e**	46	0 / 100	**8e**	54	0 / 100
6	**1f**	Me	Me	**4f**	55	-	**8f**	-[b]	-
7	**1g**	-$(CH_2)_5$-		**4g**	49	-	**8g**	-[b]	-
8	**1b**	Et	H	**5b**	57[c]	0 / 100	**9b**[d]	56	0 / 100
				5b'		0 / 100	**9b'**[d]	65	0 / 100
9	**10e**	iPr	-	**12e**	48	70 / 30	**8e**	57	75 / 25
10	**11a**	Me	-	**13a**	80	65 / 35	**14a**	47	60 / 40
11	**11c**	nPr	-	**13c**	59	70 / 30	**14c**	51	75 / 25

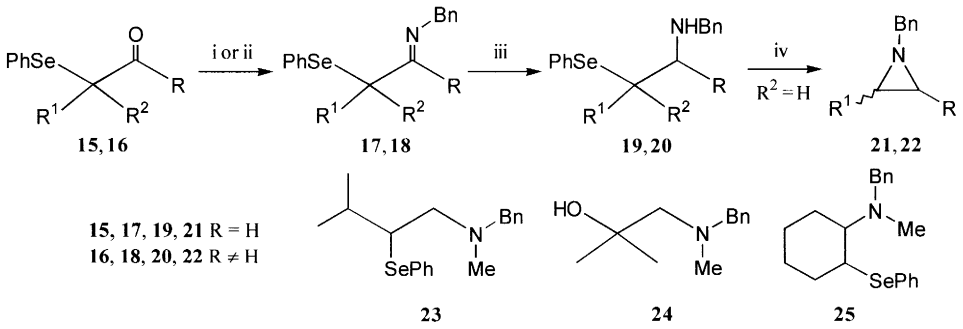
a) Isomer ratio estimated by ^1H NMR. b) Starting material recovered. c) **5b** and **5b'**, formed in equal amounts, were separated by silica gel chromatography, **5b** being the first eluted. d) C_2 and C_3 absolute configurations not assigned.

(Scheme 1, Table 1, entries 1–5). The trimethyloxonium tetrafluoroborate treatment of compounds **4** (R^2=H) followed by addition of aq. NaOH has allowed cyclisation into aziridines **8**.

The reduction of imines **2** occurred with partial deselenenylation of the substrate (5–9%) as for imines **2** (R^3=isopropyl, allyl)[12] and those derived from α-phenylselanyl aldehydes.[13] The $J_{H_2H_3}$ coupling

constant values[14] have confirmed the formation of *cis*-2,3-disubstituted aziridines **8** and led us to assign a *threo* configuration to the amino selenides **4** (R^2=H, $J_{H_2H_3}$=4 Hz). No isomerisation occurred after basic treatment of the amino selenonium salts **6**. The same two-step sequence was applied to imine **3b** derived from (*S*)-1-phenylethylamine (Table 1, entry 8). The two *threo* amino selenides **5b** and **5b′**, formed in equal amounts, were separated by silica gel chromatography and cyclised into *cis*-aziridines **9b** {$[\alpha]_D^{25}$ −50 (c 0.75 in $CHCl_3$)} and **9b′** {$[\alpha]_D^{25}$ +23 (c 1.0 in $CHCl_3$)}, respectively.

The alkyl aziridine-2-carboxylates **8e** and **14** were also obtained by cyclisation of the β-benzylamino α-phenylselanyl esters **12** (R′=Et) and **13** (R′=Me). These esters were prepared as *erythro*/*threo* mixtures from (*E*)-enoates **10** and **11**, respectively, by conjugated addition of benzylamine in the presence of PhSeCl and $ZnCl_2$, as recently described[15] (Scheme 1, Table 1, entries 9–11). *Cis*/*trans* mixtures of aziridines **8e** and **14** were obtained in ratios reflecting those of the substrates taking into account the modest yields. The prior methylation of the amino group, preventing the cyclisation, was never observed.



Scheme 2. (i) $BnNH_2$ (1 equiv.), $MgSO_4$, CH_2Cl_2, rt, 3 h (for **15a**); $BnNH_2$ (1.1 equiv.), C_6H_6 reflux Dean–Stark, 12 h (for **15b**). (ii) $BnNH_2$ (4 equiv.), $TiCl_4$ (0.66 equiv.), Et_2O, rt, 5 h (for ketones **16**). (iii) $NaBH_3CN$ (1.5 equiv.), AcOH (1 equiv.), EtOH, 0°C, 1 h. (iv) $Me_3O^+BF_4^-$ (2 equiv.), CH_2Cl_2, rt, 12 h, then 1N NaOH aq. solution

Table 2
Amino selenides **19**–**20** and aziridines **21**–**22**

Entry	Substrate				Amino selenide			Aziridine			
	N°	R	R^1	R^2	N°	Yield (%)	Erythro/Threo	N°	Yield (%)	Trans/Cis	other product
1	**15a**	H	iPr	H	**19a**	65	-	**21a**	21	-	**23** (50 %)
2	**15b**	H	Me	Me	**19b**	68	-	-	-	-	**24** (54 %)
3	**16a**	Me	H	H	**20a**	49	-	**22a**	55	-	-
4	**16b**	Et	Me	"	**20b**	55	20 / 80	**22b**	64	10 / 90[a]	-
5	**16c**	tBu	H	"	**20c**	71	-	**22c**	58	-	-
6	**16d**	Ph	Me	"	**20d**	47	0 / 100	**22d**	41	0 / 100	-
7	**16e**	-$(CH_2)_4$-		"	**20e**	57	20 / 80	-	-	-	**25** (59 %)

a) Isomer ratio estimated by GC analysis.

The situation was found to be more complex with non-functionalised amino selenides **19**–**20** prepared by reduction of imines **17**[13] derived from α-phenylselanyl aldehydes **15**[16,17] and imines **18** formed from α-phenylselanyl ketones **16**[17] (Scheme 2). A *threo* selectivity occurred in the reduction of imines **18b**, **18d** and **18e** (Table 2). The *threo* isomer of **18d**, although formed with a modest yield, was the only one isolated. The cyclisation process carried out on **19a** led to a 30/70 mixture of 1-benzyl-2-isopropylaziridine **21a** and methylamino phenylselenide **23**, resulting from a competitive methylation of the amino group. With R^1 and $R^2 \neq H$ (**19b**, R^1=R^2=Me), the *N*-methylation occurred first and the

methylselenonium group underwent hydrolysis giving the amino alcohol **24** (54% yield). The formation of aziridines **22** (Table 2, entries 3–6) was achieved from amines **20** derived from ketimines **18**. The amino selenide **20e** (20/80 *erythro*/*threo* mixture), however, has led to the *N*-methyl amine **25** (59% yield). The cyclisation into aziridine was prevented if two substituents are linked to the selenenylated carbon as for the synthesis of epoxides from β-hydroxy selenides.[7]

In conclusion, this work describes the first stereospecific synthesis of aziridines from β-alkylamino methylselenonium salts derived from β-amino phenylselenides. A total stereocontrol was observed during the reduction of imines **2** and **3** as for the reduction of the corresponding α-oxoesters **1**.[12] Work is in progress to study the scope and limitations of the cyclisation, the efficiency of other activation processes and the access to optically active aziridines.

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