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Synthesis of Azetidines by Electrophilic Selenium-Induced Cyclization of Homoallylic Benzylamines

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Abstract : Homoallyl benzylamines, prepared by allylation of the corresponding N-benzylimines, have been subjected to a selenium-induced cyclization under various conditions. At room temperature, the 4-exo and the 5-endo modes are competitive. In acetonitrile, the azetidine has been isolated as the major cyclization product, especially for homoallylamines derived from ketimines. With an excess of selenium reagent, 3-halopyrrolidines have been obtained.

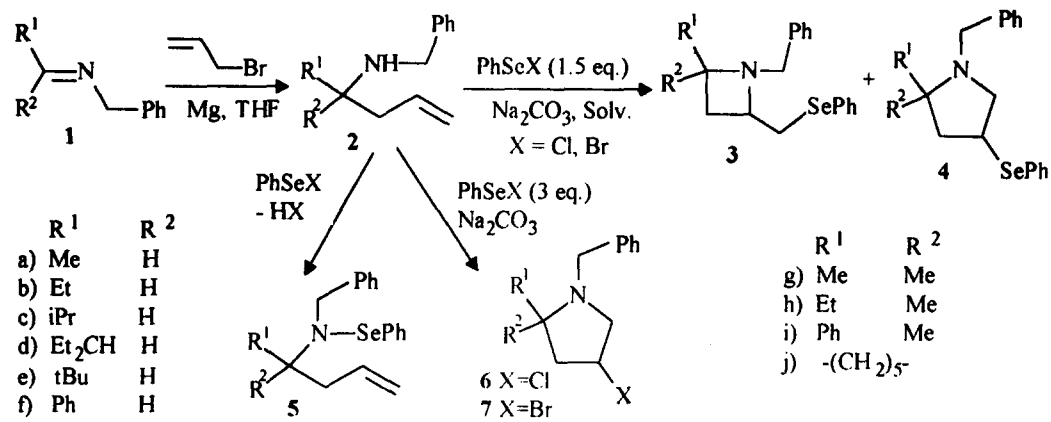
The electrophilic cyclofunctionalization of unsaturated carboxylic acids, alcohols and amines derivatives constitutes an efficient process for the synthesis of lactones, cyclic ethers and cyclic amines derivatives respectively.[1] Benzeneselenenyl halides,[1,2] N-phenylselenophthalimide,[3] benzeneselenenyl triflate[4] and benzeneselenenyl sulfate formed by oxidation of diphenyldiselenide[5] are commonly used as electrophilic reagents. The electrochemical oxidation of PhSeSePh can generate the benzeneselenenyl cation.[2,6] Pyrrolidines derivatives were synthetized from δ-unsaturated carbamates[7] and acetamides[8] through a selenium-induced 5-exo cyclization while the corresponding 6-endo mode gave piperidine derivatives as minor products. A diastereoselective version using chiral diferrocenylselenenyl bromide has been recently proposed.[9] With a hex-5-enyl carbamate, the 6-exo mode has led to the exclusive formation of piperidines.[10] Similarly the 5-endo selenium-induced cyclisation of O-allyl hydroxylamines,[11a] O-allyl oximes[11b] has given isoxazolidines. The same mode is efficient for the synthesis of N-hydroxy γ-lactams,[11c] N-acyl isoxazolidines,[11d] N-acetyl pyrazolidines[11e] and N-acyl pyrrolidin-2-ones.[12] Although little is known about the reactivity of simple δ-unsaturated primary or secondary amines, the synthesis of some pyrrolidines has been described.[13, 14]

As predicted by the Baldwin's rules,[15] the 4-exo-trig cyclization is favoured with respect to the 5-endo one but scarce reports have described the synthesis of 4-membered heterocycles. Using a selenium-induced cyclization, Murata and Suzuki have obtained 4-phenylselanyl but-2-enoic acid from but-3-enoic acid[4a] and 4-phenylselanyl butane-1,3-diol from but-3-en-1-ol.[4b] An unstable β-lactone and an oxetane were respectively proposed as intermediates. Recently, it was shown that oxetane derivatives are, in part, the kinetic 4-exo cyclization products of 2-hydroxyethyl episulfonium ions, under non-acidic conditions.[16] The 5-endo mode leading to tetrahydrofurans was only observed for the selenium-induced cyclization of homoallylic alcohols.[17]

In the course of a study of homoallylic amines derived from α-phenylselanyl N-alkyl imines, we have noted that azetidines and pyrrolidines are formed in reactions with PhSeCl or PhSeBr.[18] We decided to study the behaviour of simple homoallylic benzylamines **2**. To our surprise, we observed that, except for **2a**, the azetidine **3** was the major product in acetonitrile, especially when two substituents are present on the

homoallylic carbon. (Scheme, Table). To our knowledge, the formation of the azetidine ring by an electrophile-induced cyclization was observed for the first time.

Scheme

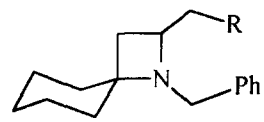


	R^1	R^2
a)	Me	H
b)	Et	H
c)	iPr	H
d)	Et_2CH	H
e)	tBu	H
f)	Ph	H

	R^1	R^2
g)	Me	Me
h)	Et	Me
i)	Ph	Me
j)	$-(CH_2)_5-$	

The homoallylamines **2**, prepared by addition of allylmagnesium chloride on imines **1**,[18] are more easily obtained in a Barbier-like reaction using **1**, allyl bromide and Mg in THF.[19] The cyclisation of **2** was achieved with PhSeCl or PhSeBr at room temperature in CH_2Cl_2 or CH_3CN containing sodium carbonate. The formation of **3** and **4** required 16 h of stirring. Sometimes, the conversion was incomplete, especially with PhSeCl, and a small amount of amine **2** was left in the reaction mixture (Table). It must be noticed that addition of silicagel was not required to achieve the cyclization as for unsaturated amine derivatives.[7b, 8, 10, 14]

The inspection of the table shows that a better ratio of azetidine **3** was obtained when X = Cl but the overall yield of cyclization was lower than for X = Br (entries 1 to 18). The steric hindrance around the α-carbon favours the formation of the azetidine **3** especially for amines **2** derived for ketimines (entries 19 to 22). In CH_3CN, the cyclization was improved and azetidines **3h** and **3i** (entries 20 and 21) were the only products with PhSeBr.[22] In these conditions, the spiroazetidine **3j** was isolated in 82 % yield (entry 22). Reductive elimination of the PhSe group of **3j** (Ph_3SnH, AIBN, toluene, Δ, 16 h) has led to the cyclohexanespiro-2 (1-benzyl 4-methyl azetidine) **8** in 61 % yield. The cis stereochemistry of the unique isomer isolated ($R^1 \neq R^2$) was deduced from NOESY experiments achieved on **3e**.



3j R = SePh **8** R = H

No traces of selenenamide **5** were detected. The incomplete cyclization, sometimes observed, can be attributed to a partial formation of **5** hydrolyzed during the work-up, giving back the amine **2**. This competitive reaction explains the need of an excess of selenium reagent. We have also observed that three equivalents of PhSeX led to the corresponding halopyrrolidines **6** (X=Cl) and **7** (X=Br).[22] (Scheme, Table). No trace of azetidine was found beside **6** or **7**. We have confirmed, in a separate experiment, that the PhSeBr treatment of the phenylselanylpyrrolidine **4c** led to the bromopyrrolidine **7c**. The substitution of the PhSe group can be easily explained by a selenophilic reaction with the reagent. We also observed that the azetidines **3** are not

intermediates in the formation of halopyrrolidines **6** or **7**. The direct formation of **6** and **7** is more complicated that expected. The assignement of the cis/trans stereochemistry of pyrrolidines **4**, **6** and **7** is also complex as for 3-phenylselanyl tetrahydrofurans,[17] and is now under investigation. Work is in progress to extend this study to various substituted and functionalized homoallylamines and to explore the chemistry of these new azetidines **3**.

Table

Selenium-induced cyclization of homoallyl benzylamines[22, 23]

Entry	Imine **1**	R^1	R^2	Amine **2**[a] Yield (%)	Cyclization X	Solvent	Conv. (%)	Ratio **3/4**	Isolated Yield (%) **3**	**4**[b]	**6** or **7**[b] PhSeX (3 eq)
1	**1a**	Me	H	65	Cl	CH_2Cl_2	80	25/75			82[d]
2	**1a**	Me	H		Br	CH_2Cl_2	95	16/84			
3	**1a**	Me	H		Br	CH_3CN	95	28/72	15	37	
4	**1b**	Et	H	74	Cl	CH_2Cl_2	88	52/48			
5	**1b**	Et	H		Br	CH_2Cl_2	100	18/82		38	69[c]
6	**1b**	Et	H		Br	CH_3CN	75	54/46	31	15	
7	**1c**	iPr	H	79	Cl	CH_2Cl_2	85	60/40	23	10	
8	**1c**	iPr	H		Br	CH_2Cl_2	100	22/78	19	31	
9	**1c**	iPr	H		Br	CH_3CN	100	65/35	51	19	77[d]
10	**1d**	Et_2CH	H	71	Cl	CH_2Cl_2	90	69/31			
11	**1d**	Et_2CH	H		Br	CH_2Cl_2	98	33/67	19	35	
12	**1d**	Et_2CH	H		Br	CH_3CN	95	72/28	61	11	
13	**1e**	tBu	H	77	Cl	CH_2Cl_2	90	63/37			75[d]
14	**1e**	tBu	H		Br	CH_2Cl_2	100	32/68	19	35	
15	**1e**	tBu	H		Br	CH_3CN	88	66/34	53[c]	18	
16	**1f**	Ph	H	81	Cl	CH_2Cl_2	87	69/31			
17	**1f**	Ph	H		Br	CH_2Cl_2	97	35/65		38	
18	**1f**	Ph	H		Br	CH_3CN	95	70/30	62	16	83[d]
19	**1g**	Me	Me	60	Br	CH_3CN	70	86/14	50	6	
20	**1h**	Et	Me	63	Br	CH_3CN	77	100/0	55	-	
21	**1i**	Ph	Me	62	Br	CH_3CN	73	100/0	58[c]	-	
22	**1j**	$-(CH_2)_5-$		49	Br	CH_3CN	100	88/12	82	10	81[d]

a) Not optimized overall yield from the carbonyl compound. b) Cis/trans isomer mixtures. c) The cis stereochemistry was attributed from NOESY experiments. d) Reaction carried out in CH_3CN. e) Reaction carried out in CH_2Cl_2.

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20. The angle-compression effect would favor the 4-membered ring formation.[21]
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22. General procedure : PhSeBr (0,708 g, 3 mmol.) in CH_3CN (50 ml) was added in one hour at room temperature to the homoallylic amine **2** (2 mmol.) in the same solvent (10 ml) containing sodium carbonate (400 mg). The mixture was stirred for 16 h and treated with a NaCl solution. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 ml). The work-up has led to an oily residue chromatographied on silicagel. An hexane elution allowed the elimination of PhSeSePh. One isomer of the pyrrolidine **4** was first separated (hexane/CH_2Cl_2 : 80/20) then the azetidine **3** and the second isomer of the pyrrolidine **4** (hexane/CH_2Cl_2 : 70/30). With 3 equivalents of PhSeBr (or PhSeCl), the pyrrolidine **7** (or **6**) was obtained as a mixture of cis/trans isomers which were separated by chromatography. The isomer ratios of compounds **4** are dependent on the nature of R^1 (R^2 = H) and are near to 70/30 for **6** and **7**.
23. The compounds **2**, **3**, **4**, **6** and **7** were isolated in a pure form and characterized by ^1H and ^{13}C NMR.

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