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Selenium Induced Stereoselective Cyclization of N-protected 3-hydroxy-4-pentenylamines

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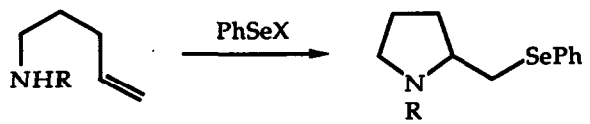
Abstract: The selenium induced cyclofunctionalization of N-protected 3-hydroxy-4-pentenylamine occurs regio- and steroselectively to give N-protected cis-2-(selenomethyl)-3-hydroxypyrrolidines in high yield. The rate of reaction and degree of stereoselectivity is shown to be dependent on the nature of the selenium reagent, reaction temperature and solvent.

The cyclofunctionalization[1] of unsaturated carbamates and unsaturated amides **1** using benzeneselenenyl halides is known to proceed readily in the presence of silica gel to afford pyrrolidine **2** and piperidine derivates[2] (e.g. scheme 1).

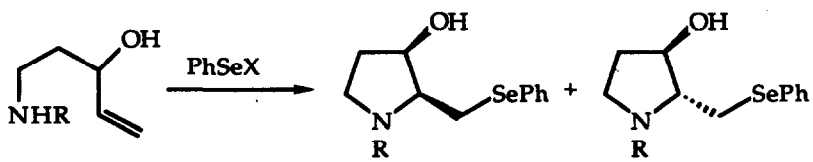


(1) **(2)**

R= CO_2Et, $COCH_3$

Scheme 1

The concomitant incorporation of the synthetically versatile seleno moeity has enabled futher elaboration of these products as intermediates in a variety of syntheses of nitrogen heterocycles.[3] The use of selenium reagents as mediators of stereoselective cyclization however, has received little attention.[4] Accordingly, we wished to examine whether reagents such as benzeneselenenyl chloride and benzeneselenenyl bromide would effect a stereoselective cyclization, arising from 1,2 asymmetric induction of substrates such as **3** (scheme 2).



(3) **(4)** **(5)**

a: R=CO_2Et, **b**: R=CO_2tBu, **c**: R=$SO_2C_6H_4CH_3$, **d**: R=$COCH_3$

Scheme 2

The carbamates **3a** and **3b**, the sulfonamide **3c** and the amide **3d** were reacted with a slight excess of the benzeneselenenyl halide in the presence of dry silica gel as catalyst and anhydrous potassium carbonate as an acid trap. Reaction times and product ratios were determined by following the reaction by reverse phase HPLC and by examination of ^{1}H n.m.r. data.[5]

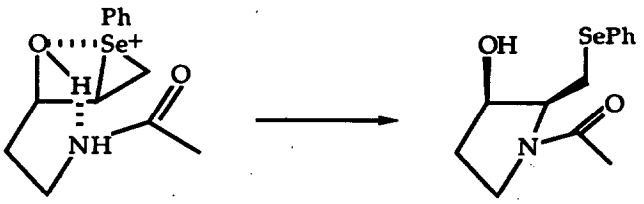
The results show that in all cases cyclization proceeds regioselectively to give only the five membered ring adducts and with good diastereoselectivity (Table). The reaction appears to be under kinetic control as product ratios do not alter with time and the separated diastereomers do not interconvert when resubjected to the reaction conditions.

Table : Selenium induced cyclization of N-protected 3-hydroxy-4-pentenylamines

Substrate	PhSeX	Reaction conditions	Product ratio (yield)[c]
3a	Cl	CH_2Cl_2, a, 4h	**4a/5a** 75/25 (88)
		$CHCl_3$, b, 30 min	85/15 (88)
		dioxane, b, 40 min	76/24 (83)
	Br	CH_2Cl_2, a, 2 h	79/21 (95)
		$CHCl_3$, b, 20 min	87/13 (95)
	SO_4	CH_2Cl_2, a, 4 h	72/28 (84)
3b	Cl	CH_2Cl_2, a, 4 h	**4b/5b** 74/26 (56)
	Br	CH_2Cl_2, a, 2 h	80/20 (60)
		$CHCl_3$, b, 20 min	88/12 (70)
3c	Cl	CH_2Cl_2, a, 3 h	**4c/5c** 64/36 (83)
	Br	CH_2Cl_2, a, 2 h	66/34 (85)
		$CHCl_3$, b, 20 min	72/28 (84)
3d	Cl	CH_2Cl_2, a, 24 h	**4d/5d** 90/10 (21)
	Br	CH_2Cl_2, a, 16 h	>99/<1 (23)
		$CHCl_3$, b, 1 h	>99/<1 (40)

a = -78°C for 10 min then to RT, b = 0°C for 10 min then to RT, c = yield refers to isolated yield, product ratios were determined by HPLC analysis

The silyl and acetyl O-protected analogues of **3a** were subjected to the reaction conditions (a) described above. This resulted in the formation of a 1:1 mixture of diastereomers in only moderate yield and reaction proceeded at a much slower rate. These observations, together with molecular modelling studies, are in accordance with previous reports[6] in which intramolecular hydrogen bonding between the hydroxyl proton and the incoming internal nucleophile has been invoked to rationalise the stereoselective cyclization (scheme 3). The quite dramatic increase in stereoselectivity observed in the case of the acetamide, **3d**, may be attributed to the carbonyl group influencing which face of the double bond is attacked by the electrophile.[7] No such participation is apparent with the carbamates **3a** and **3b** or sufonamide **3c** due to the greater rotational freedom about the CO-N and SO_2-N bonds.[8]



Scheme 3

The counter anion of the selenium species was shown to have a marked effect on the rate and stereoselectivity of reaction. The reaction occured much faster using benzeneselenenyl bromide than with benzeneselenenyl chloride or benzeneselenenyl sulfate.[9] No reaction was observed when benzeneselenenyl phthalimide[10] was used. The bulky phthalimido group is possibly too sterically hindered to effect formation of the selenonium ion precursor to cyclization shown above. The rate and stereoselectivity of the reaction was also enhanced by the use of more polar solvents[11], which suggests that a good leaving group ability of the counter anion and the resultant rapid formation of an intermediate selenonium ion is responsible for the fast, stereoselective reaction observed.

The stereochemistry of the products was assigned from ^{13}C n.m.r. data[12] and a series of *n*OE experiments in which a 4.1% enhancement was observed between H_2 and H_3 of **4c**, as compared to 0.5% for the same hydrogens of **5c**. The carbamate **4a** was obtained in crystalline form suitable for X-ray analysis, which clearly depicts the *cis* relationship of the substituents at C_2 and C_3.

Work is currently being directed towards extension of the methodology to the formation of substituted piperidines and elaboration of these products to biologically active indolizidine alkaloids.

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5. All spectral and microanalytical data obtained were consistent with the structures proposed.

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11. Reaction occurred cleanly using dichloromethane, chloroform, or dioxane as solvent, however only starting materials were recovered using acetonitrile.

12. In all cases the C-Se resonance of the *cis* diastereomer in the ^{13}C n.m.r. spectra was shifted 3-5 ppm upfield relative to the corresponding *trans* isomer. See Wehrli F. W., Wirthin T., Interpretation of Carbon 13 NMR Spectra; Heydon and Son, London, 1980.

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