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Selenium Induced Stereoselective Cyclization of N-substituted-4-hydroxy-5-hexenylamines

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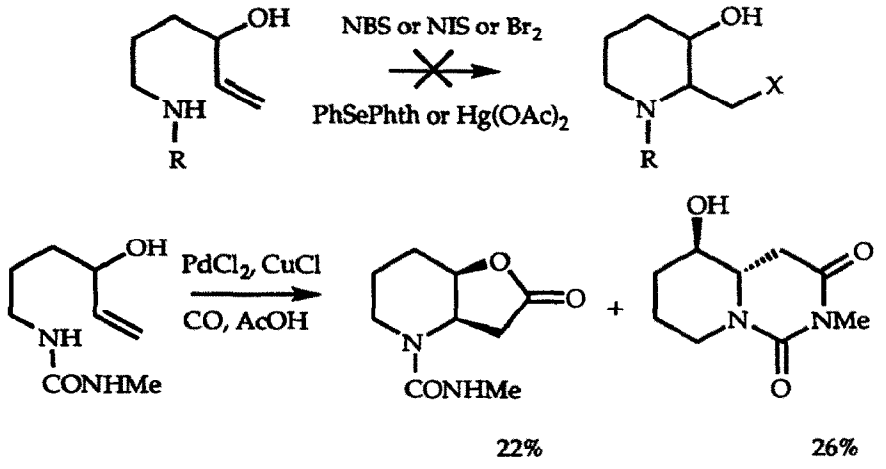
Abstract: *The selenium induced cyclization of N-substituted 4-hydroxy-5-hexenylamines occurs regio- and stereoselectively to give N-substituted trans-2-(phenylselenomethyl)-3-hydroxypiperidines in moderate yield. Synthesis of the biologically active diol (8) was achieved via oxidation of the phenylseleno moiety to the phenylselenone and subsequent displacement with sodium hydroxide.*

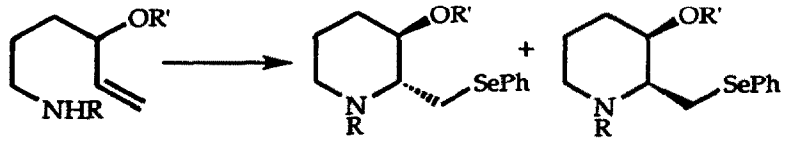
Unsaturated carbamates and amides are known[1] to undergo a facile cyclization in the presence of benzeneselenenyl halides and silica gel to afford substituted pyrrolidines and piperidines. We have recently reported[2] the selenium induced cyclization of 3-hydroxy-4-pentenylamines and now describe the application of this methodology to the synthesis of subtituted hydroxypiperidines.

Whilst there are many examples of the cyclization of N-substituted-3-hydroxy-4-pentenylamines using a variety of electrophilic reagents,[3-8] 4-hydroxy-5-hexenylamines have proved comparatively unreactive.[7,8] In the few cases in which cyclizations have occurred[7] product mixtures were obtained or the reaction occured non-stereoselectively (scheme 1).



Scheme 1

We have found that carbamates, sulfonamides and amides of 4-hydroxy-5-hexenylamines all react with benzeneselenenyl halides in the presence of silica gel and anhydrous potassium carbonate to give predominately *trans*-2-(phenylselenomethyl)-3-hydroxypiperidines in moderate yield (Table and scheme 2).



1 2 3

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

e: R=$SO_2C_6H_4CH_3$, R'=TBDPS

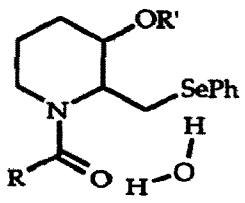
Scheme 2

Table: Selenium Induced Cyclization of Substituted 5-Hexenylamines

Substrate	Reaction conditions[1]	Product yield (ratio 2:3)[2]
1a	a, 48 h	57% (3:1)
	b, 18 h	61% (5:1)
1b	a or b, 5 days	No reaction
1c	a, 48 h	59% (3:1)
	b, 18 h	58% (5:1)
1d	a, 48 h	41% (3:1)
1e	a, 5 days	27% (3:1)

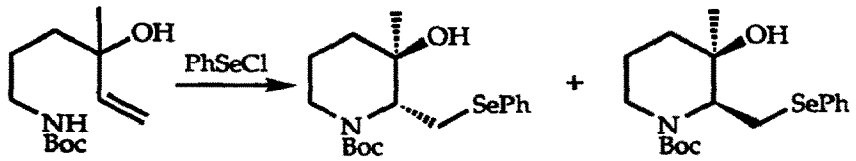
1. a = PhSeCl, CH_2Cl_2, -78°C ,10 min. then to RT; b = PhSeBr, $CHCl_3$, 0°C, 10 min. then to RT.
2. yield refers to isolated yield, product ratios were determined by HPLC analysis

The reaction is slow and presumably under thermodynamic control, in contrast to the fast, kinetically controlled stereoselective *cis* cyclization of N-substituted pentenylamines[2]. Compounds (2a), (2d) and (2e) could be isolated as stable crystalline hydrates after extended reaction times, or upon exposure of the corresponding selenide to THF/water at room temperature. These have been assigned[9] the general structure (4).



4

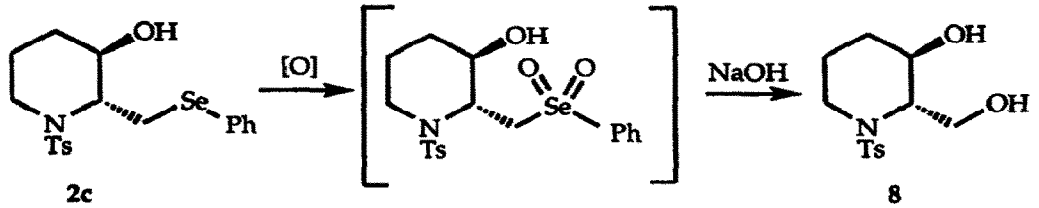
In an attempt to increase the stereoselectivity of reaction the O-protected silyl ether (1e) was subjected to the above conditions, however the product ratio obtained was the same as that for the alcohol (1c). Although the t-butylcarbamate (1b) would not cyclize, the 4-hydroxy-4-methyl t-butylcarbamate (5) underwent clean reaction to give a 3:1 mixture of diastereomers (6) and (7) in good yield (scheme 3). In this case the stereochemistry of the major isomer (6) was elucidated from the nOE enhancement seen between the methyl resonance and the two diastereotopic hydrogens adjacent to selenium. No enhancement was observed to the proton adjacent to nitrogen.



5 6 7

Scheme 3

The selenide (2c) was converted to the *trans*-3-hydroxy-2-(hydroxymethyl)piperidine (8) *via* conversion to the selenone using MCPBA followed by an *in situ* nucleophilic displacement with aqueous sodium hydroxide (scheme 4). We are currently investigating the generality of this *in situ* displacement of selenones by nucleophiles.[10]



2c 8

Scheme 4

Compounds such as (8) and other N-protected analogues thereof are powerful antagonists of immunosupressants isolated from the blood serum of tumour bearing mice.[11]

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