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Synthesis of pyrrolidinols by radical additions to carbonyls groups†

Francesca Marini *, Martina Palomba, Luana Bagnoli and Claudio Santi

Department of Pharmaceutical Sciences, University of Perugia

* Correspondence: francesca.marini@unipg.it

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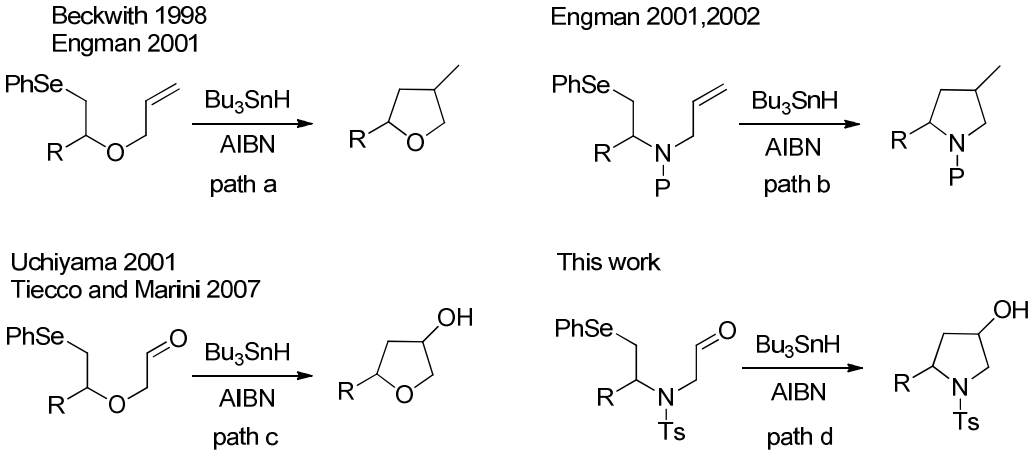
Abstract: Radical cyclizations represent powerful synthetic strategies for the assembling of heterocycles. Most radical cyclizations are based on the addition to C-C double or triple bonds. On the contrary, the addition to C-O double bonds is rarely reported, since it proceed reversibly due to the formation of thermodynamically unfavorable alkoxy radicals. Herein we report our attempts to construct substituted pyrrolidin-3-ols by tin-mediated radical cyclization of 5-phenylseleno-3-aza-pentanals. These rings are widely represented in natural products and drug candidates with various biological activities.

Keywords: Selenium; cyclizations; pyrrolidines; radicals.

1. Introduction

Radical cyclizations are considered effective procedures for the assembling of five membered heterocycles [1,2] with useful applications in the stereoselective synthesis of natural and/or biologically active compounds. Often, the cyclization occurs via an intramolecular addition of a carbon-centered radical to C-C double bonds. Arylselenides have been widely employed as radical precursors in tin hydride-mediated reactions due to the high synthetic accessibility, the good functional group tolerance and the easy homolytic cleavage of the weak C-Se bond [3-4]. In fact, even if the phenylselenyl groups can be removed by $Bu_3Sn•$ at rates comparable to those of a bromine they are more stable to most synthetic transformations and can be introduced in the molecule early in the synthetic sequence. Scheme 1 shows examples of synthesis of tetrahydrofurans [5-7] and pyrrolidines [8-10] starting from 3-oxa or 3-aza-5-hexenyl radicals via a 5-*exo-trig* cyclization paths.



Scheme 1. Examples of radical cyclization for the synthesis of tetrahydrofurans and pyrrolidines

Good yields, excellent regioselectivity and a poor to good level of diastereocontrol were observed depending on the structure of the starting compounds, the nature of hydrogen donor, the type of protecting group, and the presence of Lewis acids (path a and b). Other cyclizations involve intramolecular radical addition to conjugated alkenes or allenes [11,12]. On the contrary, radical cyclizations by addition to other multiple bonds, i.e. C=O bonds, is less common [13]. Even if the addition of the carbon radical to a carbonyl group is faster than that to a carbon-carbon double bond it is not easy to trap the alkoxy cyclic radical. In fact β-scission reactions can occur generating more stable open chain intermediates. At this purpose, few years ago we reported the stereoselective synthesis of tetrahydrofuran-3-ols by means of a tin-mediated radical cyclization of 5-phenylseleno-3-oxa-pentanals (scheme 1, path c) [14]. As a continuation of this work and part of our studies in the use of selenium reagents for the synthesis of heterocycles of biological interest [15-18], we now report our attempts to construct pyrrolidin-3-ols using 5-phenylseleno-3-aza-pentanals as radical precursors (scheme 1, path d). 3-Hydroxylated pyrrolidines were identified in several natural products and compounds of pharmaceutical interest. Representative examples are reported in figure **1**: the bioactive metabolite of Kainic acid **I**, isolated from the red alga *Digenea simplex* [19], the (+)-Preussin (II) isolated from fermentation broths of *Aspergillus ochraceus* and *Preussia sp*, with antibiotic and cytotoxic activities against different human tumor cell lines [20], and the Asciminib (**III**) [21], an allosteric ABL 1 Tyrosine kinase inhibitor clinical candidate for the treatment of chronic myelogenous leukemia, are reported.

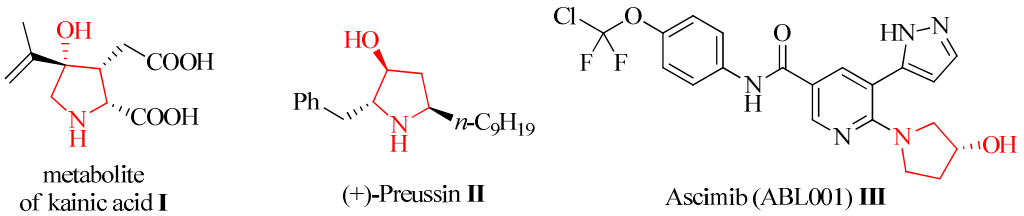
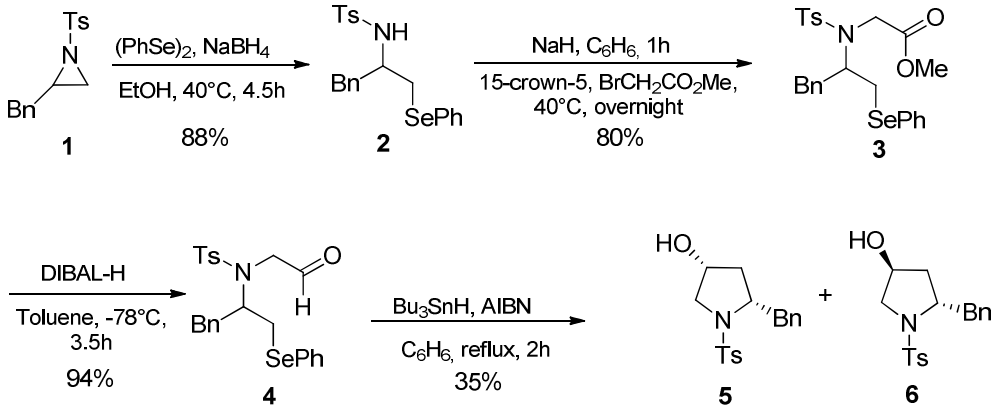


Figure 1. Bioactive compounds containing a pyrrolidin-3-ol core.

2. Results and Discussion

The synthesis of the radical precursor **4** was obtained in three steps starting from the N-Tosyl-2-benzylaziridine **1** (scheme 2) adapting literature procedures [8,14]. The highly regioselective ring opening of the aziridine **1** by the nucleophilic species generated *in situ* by diphenyldiselenide and $NaBH_4$ in ethanol, afforded the selenide **2** in excellent yield.



Scheme 2. Synthesis of pyrrolidin-3-ols **5** and **6**

Then, the alkylation of the nitrogen atom was carried out in the presence of methyl bromoacetate to furnish the intermediate **3** in good yield. The partial reduction of ester **3** to aldehyde **4** was performed in excellent yield with DIBAL-H. This compound was then submitted to the radical cyclization by treatment with a slight excess of tributyltin hydride in the presence of a catalytic amount of AIBN in refluxing benzene. Pyrrolidin-3-ols **5** and **6** were obtained in a modest yield as a mixture 62:38 of the *cis* and *trans* isomers. The two diastereoisomers were separated by medium pressure column chromatography. The stereochemical attribution was made by NOESY experiment (Figure 2).

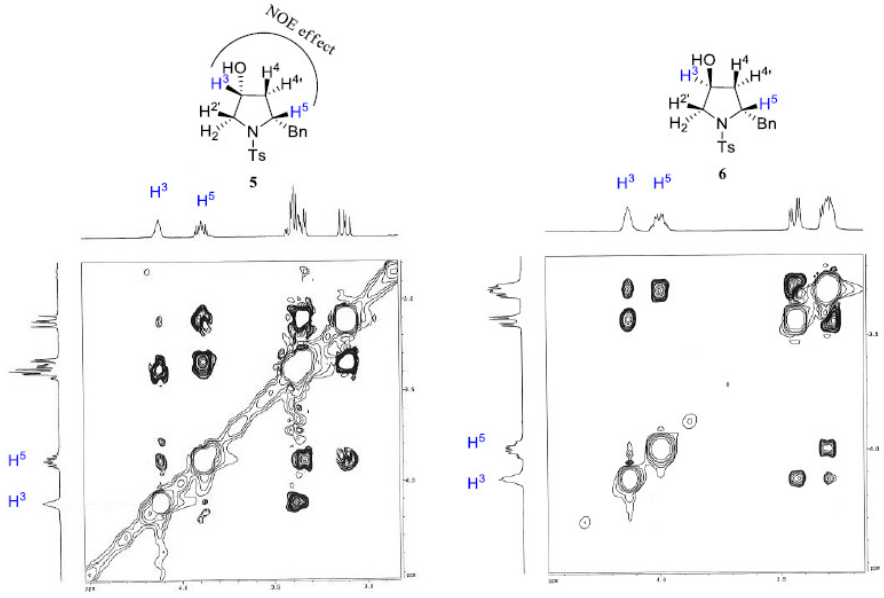
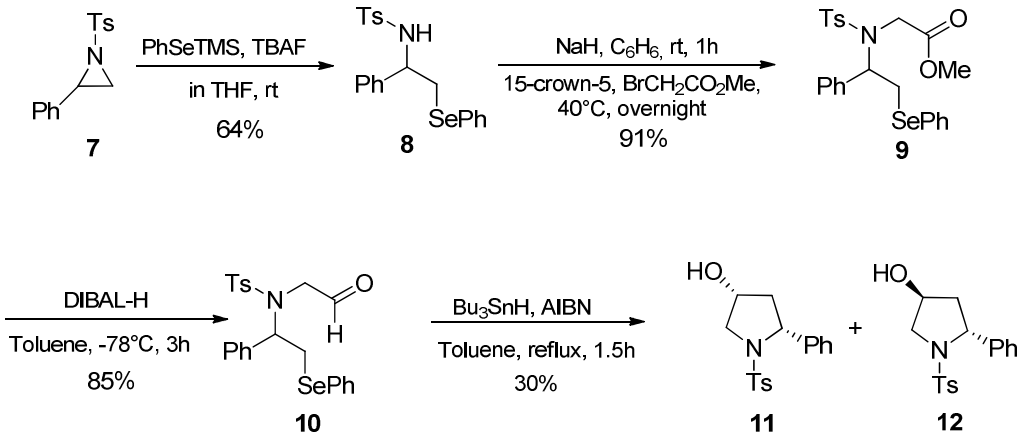


Figure 2. Selected 2D NOESY correlations for pyrrolidin-3-ols **5** and **6**.

Observation of the NOE cross peak in the 2D NOESY spectrum indicated the spatial proximity of the C-3 and C-5 methine hydrogens of the major diastereomer **5**. The cross peak is absent in the minor isomer **6** as expected for a *trans* 3,5-disubstituted pyrrolidine.

Further experiments were carried out in order to optimize the yields. We explored several conditions varying the amount of Bu_3SnH, the nature of the H-donor (Ph_3SnH) and the solvent. Unfortunately, no improvement was obtained.

The procedure was also applied to the synthesis of 5-phenyl substituted 3-pyrridinols (Scheme 3).



Scheme 3. Synthesis of pyrrolidin-3-ols **11** and **12**

In this case the ring opening of the aziridine **7** was performed with $PhSeSi(Me)_3$ generated *in situ* from diphenyldiselenide, NaH and trimethylsilyl chloride under reflux. The β-amino selenide **8** isolated by medium pressure chromatography was obtained in 64% yield. A 30% of the regioisomer was also recovered. This reaction proceeds with better yield and regioselectivity than those obtained in similar processes carried out with other nucleophilic selenium species. Successively, the usual alkylation followed by the partial reduction of the ester **9** gave the aldehyde **10**. The radical cyclization carried out using Bu_3SnH and AIBN lead to mixture of compounds **11** and **12** with a slight preference for the *cis* isomer (58:42 after column chromatography). The mixture of the 3-pyrrolidinols was separated by medium pressure chromatography and structurally attributed by NOESY experiments.

3. Conclusions

The synthesis of 3-hydroxylated pyrrolidines via intramolecular addition of carbon radicals to aldehydes has been carried out. Radicals derived from **4** and **10** undergo 5-*exo*-*trig*-cyclizations to afford mixtures of *cis* and *trans* 5-substituted-pyrrolidin-3-ols in poorer yields than those observed in similar cyclizations to tetrahydrofuranols. Further investigations with selenium reagents for the synthesis of biologically active pyrrolidine derivatives are currently underway.

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Conflicts of Interest: The authors declare no conflict of interest.

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