



A general approach for the synthesis of 5-substituted-4-amino-pyrrolidin-2-ones and 5-substituted-4-amino-3-pyrrolin-2-ones

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ABSTRACT

Short stereoselective syntheses of both 5-substituted-4-amino-pyrrolidin-2-ones and 5-substituted-4-amino-3-pyrrolin-2-ones from natural α -amino acids are described.

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Cyclic diamino acids derivatives like 4-amino-pyrrolidin-2-ones and 4-amino-3-pyrrolin-2-ones are recognized to be of biological importance (Fig. 1). Indeed, 4-amino-pyrrolidin-2-ones are described as peptidomimetics,¹ as structural sub-units of natural products,² as useful precursors of γ -lactam bridged dipeptides,³ and in the structures of renin-inhibiting peptides.⁴ In addition, 4-amino-pyrrolidin-2-ones are important intermediates for the syntheses of 3-aminopyrrolidines, which are ubiquitous systems found in natural products as alkaloids and in a diverse number of compounds displaying an impressive range of biological activities.⁵ Also, 3-aminopyrrolidines were recently employed as useful organocatalysts in asymmetric Mannich reactions.⁶ Furthermore, 4-amino-pyrrolidin-2-ones provide an excellent synthetic entry into β,γ -diaminoacids, that have been subject of growing interest due to their biological properties.^{7,8}

Although natural products containing the 4-amino-3-pyrrolin-2-one unit (β -amino-unsaturated lactams) are unknown, to the best of our knowledge, some compounds of this class have been of interest due to their biological properties as herbicidal,⁹ for the treatment of epilepsy, anxiety, and tension,¹⁰ as antibacterial¹¹ or hypoglycemic,¹² and as dipeptide analogues.¹³

Some examples are shown in Figure 2. While lactams **1** are sub-units of antifungal and cytotoxic natural cyclic hexapeptides microscloerodermis,² the highly active antipsychotic agent nemonapride has been commercialized under its racemic form.¹⁴ Peptides containing 3-amino-deoxystatine have better renin inhibitory activities than those derived from statine,⁸ which is a component of the aspartyl protease inhibitor pepstatin. The pyrro-

lin-2-one **2** and the benzotiazepine **3** have, respectively, herbicidal⁹ and antibacterial activities.¹¹

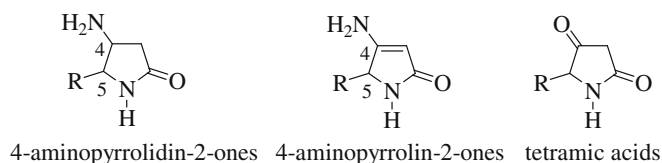


Figure 1. 4-amino-pyrrolidin-2-ones and 4-amino-3-pyrrolin-2-ones.

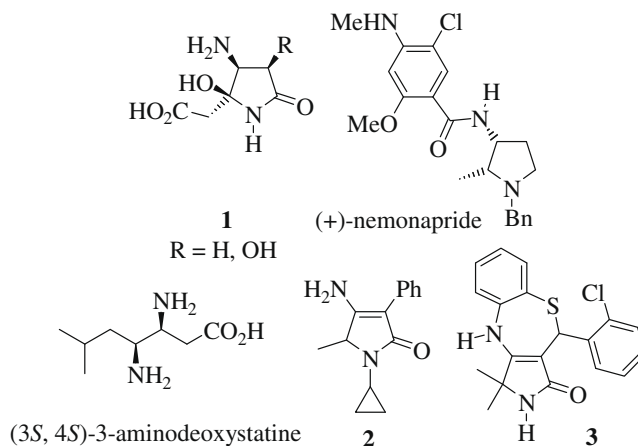


Figure 2. Some biologically active β -amino lactams.

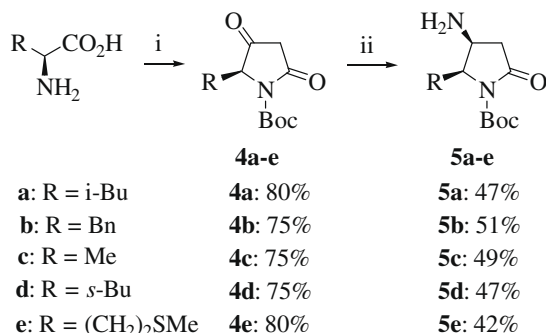
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In spite of the growing interest in both 4-amino-pyrrolidin-2-ones and 4-amino-3-pyrrolin-2-ones, few routes have been described to the stereoselective syntheses of these kind of compounds. Indeed, the few methods reported for the synthesis of 4-amino-3-pyrrolin-2-ones suffer from the lack of generality and include nucleophilic substitution of tetramic acids derivatives by amines,^{10,12,13} ring closure from azadienes,¹⁵ ring expansion of azirines,¹⁶ Dieckmann cyclization,¹⁷ and conjugate addition of azide to an unsaturated lactam followed by treatment with trifluoroacetic acid,¹⁸ among other methods.¹⁹

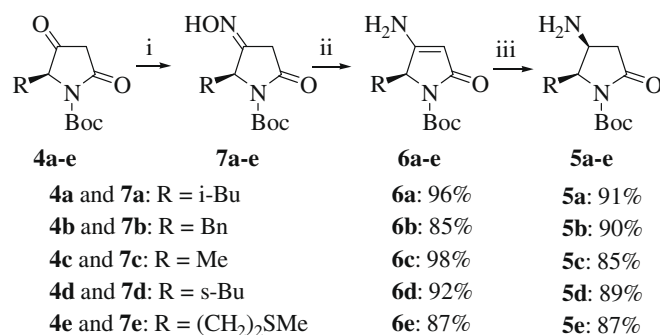
Typical routes to 5-substituted-4-amino-pyrrolidin-2-ones described so far include alkyl radical addition-cyclization of oxime ethers,²⁰ the Beckmann rearrangement of oximes,²¹ the intramolecular rearrangement of β -lactams,²² and conjugate addition of amines to both enoates²³ and to bicyclic pyrrolidin-2-ones (unsaturated lactams).^{5c,24} More recently, a multistep asymmetric synthesis of *anti*-5-isopropyl-4-amino-pyrrolidin-2-ones from α -amino acids was described.²⁵ Although tetramic acids can be considered as attractive starting materials for the stereoselective syntheses of 5-substituted-4-amino-3-pyrrolidin-2-ones, Tønder and co-workers reported that the direct reductive amination of tetramic acids with amino acids failed to reach these heterocyclic compounds.¹³ In fact, they had to employ a stepwise procedure comprising enamine formation from tetramic acids and protected amino acids followed by hydrogenation to prepare peptide derivatives of *syn*-5-alkyl-4-amino-pyrrolidin-2-ones.

Herein we are pleased to report a procedure for reductive amination of tetramic acids with ammonium hydroxide/ NaBH_3CN as well as an approach based on reduction of oximes for the stereocontrolled syntheses of *syn*-5-substituted-4-amino-pyrrolidin-2-ones and 5-substituted-4-amino-3-pyrrolin-2-ones from natural α -amino acids.

The known tetramic acids **4a–e** were easily prepared in multi-gram scales and high overall yields without further purification from N-protected natural α -amino acids using the Meldrum's acid condensation method, as already described (Scheme 1).²⁶ Attempts to perform one-pot direct reductive amination of **4a** using NaBH_3CN in AcONH_4 or aniline,²⁷ $\text{NaBH}_3\text{CN}/\text{ZnCl}_2/\text{piperidine}$,²⁸ and $\text{NaBH}(\text{OAc})_3/\text{AcONH}_4$ ²⁹ failed to produce the 4-amino-pyrrolidin-2-one **5a**, suggesting a slow formation of the imine intermediate from ammonia and more substituted amines in a similar situation to that described by Tønder and co-workers.^{13a} This way, we employed an alternative stepwise protocol based on imine formation followed by in situ reduction to convert easily **4a–e** into 5-substituted-4-amino-pyrrolidin-2-ones **5a–e**. These products were obtained as colorless oils in acceptable yields and with total control of the stereoselectivity, after purification by flash chromatography on silica gel. All the spectral data of **5a–e** are in agreement with the literature for both closely related 5-substituted-4-hydroxy-pyrrolidin-2-ones^{26b} and 4-alkylamino-pyrrolidin-2-ones.^{13b}



Scheme 1. Reagents and conditions: (i) See Ref. 26; (ii) NH_4OH , HOAc, benzene, reflux, 6 h then NaBH_3CN , HOAc, rt, 2 h.



Scheme 2. Reagents and conditions: (i) $\text{NH}_2\text{OH}\cdot\text{HCl}$, NaHCO_3 , Na_2SO_4 , CH_2Cl_2 , rt, 48 h; (ii) MoO_3 , NaBH_4 , MeOH, rt, 6 h; (iii) NaBH_3CN , HOAc, rt, 2 h.

The stereochemical assignments of the newly created stereogenic centers in **5a–e** were made on the basis of nOe NMR spectra and the proposed absolute configurations are in agreement with the products from reduction of **4a–e** described in the literature.²⁶ For example, starting from **H₄** of **2b**, a significant nOe was observed with **H₅** (9.7%), which implies a *syn* relationship between the substituents in positions 4 and 5. Next, based on the preparation of dipeptide analogues derived from 4-alkylamino-pyrrolin-2-ones from tetramic acids and protected amino acids,¹³ we turned attention to synthesize 5-substituted-4-amino-3-pyrrolin-2-ones **6a–e** from tetramic acids (Scheme 2). Reactions of **4a–e** with hydroxylamine furnished the corresponding oximes **7a–e** (as mixtures of *E*- and *Z*-isomers)³⁰ as yellow oils in quantitative yields and high purities. The subsequent reactions of **7a–e** with NaBH_4 in the presence of MoO_3 ³¹ led to good yields of the corresponding imines, which are in equilibrium with the 5-substituted-4-amino-3-pyrrolin-2-ones **6a–e**.¹⁵ Also, in these cases the compounds **6a–e** were sufficiently pure to be used in the next step without further purification. Upon reduction with NaBH_3CN in HOAc, the pyrrolin-2-ones **6a–e** produced the corresponding lactams **5a–e** in good yields and high purity.³²

In conclusion, although both methods disclosed in this Letter are limited to producing primary amines, they allowed an easy production of 5-substituted-4-amino-pyrrolidin-2-ones and 5-substituted-4-amino-3-pyrrolin-2-ones from different natural α -amino acids using simple protocols. The latter compounds were easily converted in the former by reduction with NaBH_3CN .

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Supplementary data

Supplementary data (experimental procedures, characterization data, ^1H and ^{13}C NMR for all new compounds) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2009.03.003](https://doi.org/10.1016/j.tetlet.2009.03.003).

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