Tetrahedron Letters 50 (2009) 2402–2404

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Sergio Pinheiro [a,*], Ronaldo C. da Silva Júnior [a], Acácio Silva de Souza [a], José Walkimar de M. Carneiro [b], Estela M. F. Muri [c], O. A. C. Antunes [d]

[a] Departamento de Química Orgânica, Instituto de Química, Universidade Federal Fluminense, Outeiro de S. João Batista s/n Centro 24020-141, Niterói, RJ, Brazil
[b] Departamento de Química Geral e Inorgânica, Instituto de Química, Universidade Federal Fluminense, RJ, Brazil
[c] Faculdade de Farmácia, Universidade Federal Fluminense, RJ, Brazil
[d] Instituto de Química, Universidade Federal do Rio de Janeiro, CT, Bloco A 641, 21941-970 Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article history:
Received 26 January 2009
Revised 28 February 2009
Accepted 2 March 2009
Available online 6 March 2009

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.

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 antibacterial[11] 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 microsclerodermins,[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 pyrrolin-2-one **2** and the benzotiazepine **3** have, respectively, herbicidal[9] and antibacterial activities.[11]

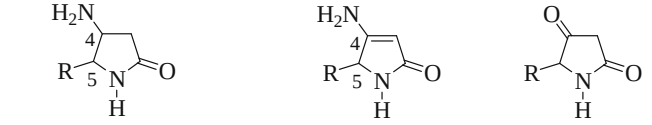


Figure 1. 4-amino-pyrrolidin-2-ones and 4-amino-3-pyrrolin-2-ones.

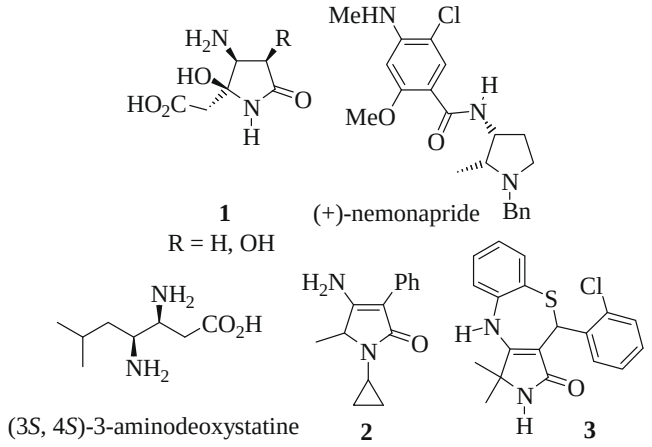


Figure 2. Some biologically active β-amino lactams.

* Corresponding author. Tel.: +55 21 26292369; fax: +55 21 26292129.
E-mail address: spinuff@gmail.com (S. Pinheiro).

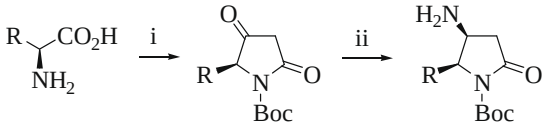
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.03.003

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 enoates[23] 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.

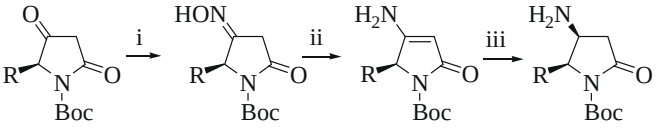
Herein we are pleasant to report a procedure for reductive amination of tetramic acids with ammonium hydroxide/$NaBH_3CN$ as well as an approach based on reduction of oximes for the stereocontrolled syntheses of *syn*-5-substituted-4-amino-pyrrolidin-2-ones and 5-substituted-4-amino-3-pyrrolin-2-ones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

The known tetramic acids **4a–e** were easily prepared in multigram 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] $NaBH_3CN/ZnCl_2$/piperidine,[28] and $NaBH(OAc)_3/AcONH_4$[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]



	4a-e	**5a-e**
a: R = i-Bu	**4a**: 80%	**5a**: 47%
b: R = Bn	**4b**: 75%	**5b**: 51%
c: R = Me	**4c**: 75%	**5c**: 49%
d: R = *s*-Bu	**4d**: 75%	**5d**: 47%
e: R = $(CH_2)_2SMe$	**4e**: 80%	**5e**: 42%

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



4a-e	**7a-e**	**6a-e**	**5a-e**
4a and **7a**: R = i-Bu		**6a**: 96%	**5a**: 91%
4b and **7b**: R = Bn		**6b**: 85%	**5b**: 90%
4c and **7c**: R = Me		**6c**: 98%	**5c**: 85%
4d and **7d**: R = s-Bu		**6d**: 92%	**5d**: 89%
4e and **7e**: R = $(CH_2)_2SMe$		**6e**: 87%	**5e**: 87%

Scheme 2. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, $NaHCO_3$, 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 H_4 of **2b**, a significant nOe was observed with H_5 (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 $NaBH_3CN$.

Acknowledgments

The authors acknowledge FAPERJ, CAPES, CNPq, and FINEP, Brazilian Financing Agencies, for financial support.

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.

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