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A Stereoselective Entry into Functionalized 1,2-Diamines by Zinc-Mediated Homologation of α-Aminoacids

Cam Thuy Hoang, Valérie Alezra, Régis Guillot,† and Cyrille Kouklovsky*

Laboratoire de Chimie des Procédés et Substances Naturelles, Institut de Chimie Moléculaire et des Matériaux d'Orsay (UMR CNRS n°8182), Bâtiment 410, Université de Paris-Sud 11, F-91405 Orsay, France

cykouklo@icmo.u-psud.fr

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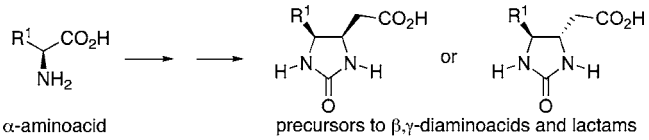
ABSTRACT



A general, stereoselective synthesis of 4,5-disubstituted imidazolidines-2-ones from α-aminoacids has been developed: the key steps are a Blaise reaction of bromoacetate on α-aminonitriles and further reduction. Although reduction with sodium cyanoborohydride afforded a mixture of cis and trans isomers 6a–e with moderate to good stereoselectivity, reduction with sodium in liquid ammonia gave the trans isomers 8a–e with complete stereoselectivity. Acidic hydrolysis of the urea gave 4-amino-pyrrolidinones, which can be precursors to *β*,*γ*-diaminoacids or 3-aminopyrrolidines.

Stereochemically defined 1,2-diamines are valuable building blocks in organic synthesis as they can be used as metal ligands, organic catalysts, and precursors to biologically relevant compounds, such as nonproteinogenic aminoacids, or alkaloids.[1] In a study related to the synthesis of statin analogues, we planned to prepare enantiomerically pure *β*,*γ*-diaminoacids, which belong to the 1,2-diamine family, in a convergent manner by homologation of α-aminoacids. *β*,*γ*-Diaminoacids are new type of aminoacid that have been the subject of growing interest, owing to their capacity to modify biological properties in small peptides.[2,3] Furthermore, cyclization of these aminoacids gives rise to 4-aminopyrrolidinone, thus providing an entry into the 3-aminopyrrolidine family of alkaloids[4] (Figure 1).

In this communication, we wish to report a general, convergent, and stereoselective approach to *syn*- or *anti*-*β*,*γ*-diaminoacids from optically active α-aminoacids by zinc-mediated homologation with the Blaise reaction, followed by reduction.

The Blaise reaction is a variant of the Reformatsky reaction with nitriles as substrates and has been described as a method for the synthesis of *β*-ketoesters from nitriles.[5] Zinc-mediated condensation of α-bromoesters onto nitriles affords an

† To whom correspondance concerning X-ray crystallography should be addressed. E-mail: regisguillot@icmo.u-psud.fr.

(1) For a review on the chemistry of 1,2-diamines: Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.

(2) (a) Schostarez, H. J. *J. Org. Chem.* **1988**, *53*, 3628. (b) Thaisrivongs, S.; Schostarez, H. J.; Pals, D. T.; Turner, S. R. *J. Med. Chem.* **1987**, *30*, 1837.

(3) Synthetic approaches to *β*,*γ*-diaminoacids: Yoo, D.; Kwon, S.; Kim, Y. G. *Tetrahedron: Asymmetry* **2005**, *16*, 3762 and references cited therein.

(4) Synthetic approaches to enantiomerically pure 3-aminopyrrolidines: Davies, S. G.; Garner, A. C.; Goddard, E. C.; Kruchinin, D.; Roberts, P. M.; Rodriguez-Solla, H.; Smith, A. D. *Chem. Commun.* **2006**, 2664 and references cited therein. See also: (a) Jean, L.; Rouden, J.; Maddaluno, J.; Lasne, M.-C. *J. Org. Chem.* **2004**, *69*, 8893. (b) Huang, P. Q.; Wang, S. L.; Ye, J. L.; Ruan, Y. P.; Huang, Y. Q.; Zheng, H.; Goa, J. X. *Tetrahedron* **1998**, *54*, 12547.

(5) (a) Blaise, E. *C.R. Hebd. Séances Acad. Sci.* **1901**, *132*, 478. (b) Kagan, H. B.; Suen, Y. H. *Bull. Soc. Chim. Fr.* **1966**, 1819. (c) For a recent review concerning the Reformatsky and Blaise reactions in synthesis: Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325.

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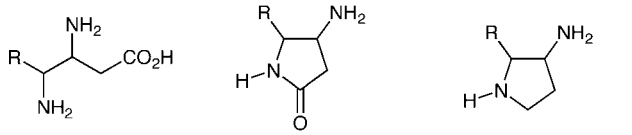


Figure 1. β,γ-Diaminoacids and corresponding pyrrolidine derivatives.

iminozincate intermediate, which is then hydrolyzed in an acidic medium to the corresponding β-ketoester. An important modification of the Blaise reaction was developed by Kishi and co-workers who reported that hydrolysis of the reaction medium with concentrated potassium carbonate afforded an enaminoester.[6] Therefore, it was anticipated that this reaction, followed by reduction of the enaminoester, could be applied to the synthesis of β-aminoacids. This strategy has been applied to the synthesis of β-lactams[7] and more recently to the synthesis of carbohydrate-derived β-aminoacids.[8,9] Our approach to the synthesis of 4-aminopyrrolidinones and β,γ-diaminoacids relies on a similar strategy that involves the preparation of α-aminonitriles from α-aminoacids, Blaise reaction, and subsequent reduction of the enaminoester (Figure 2).

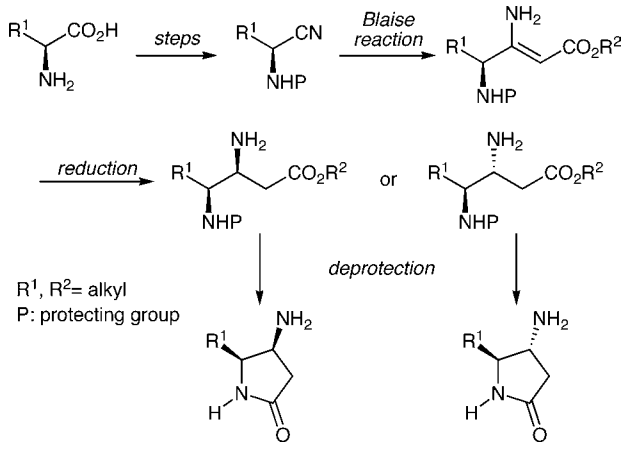
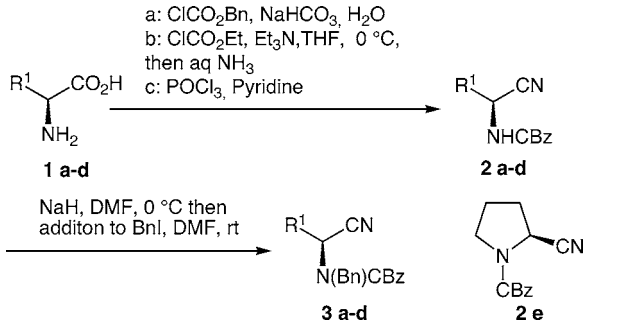


Figure 2. General approach to β,γ-diaminoacids and related γ-lactams.

N-Benzyloxycarbonyl aminonitriles **2a**−**d** were prepared as pure enantiomers[10] in three steps from the corresponding

Table 1. Synthesis of N,N-Diprotected α-Aminonitriles



entry	R^1	yield of **2** (%)	yield of **3** (%)	ee[a] (%)
a	Me	46	93	>99
b	*i*Pr	45	84	99
c	*i*Bu	43	89	>99
d	Bn	55	91	>99

[a] Determined by HPLC.

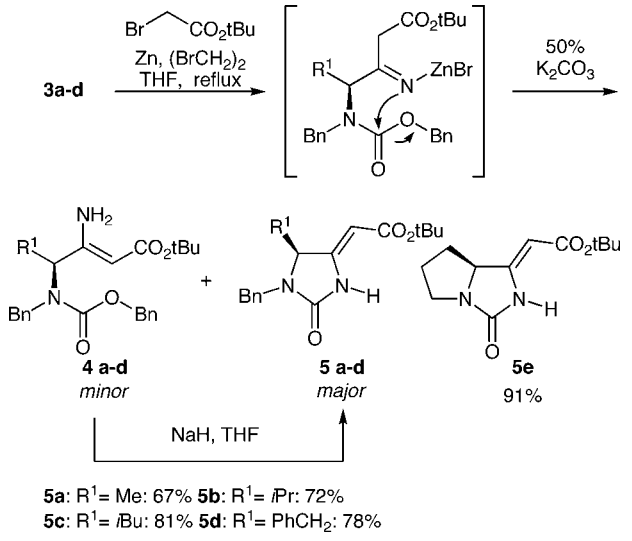
L-α-aminoacids **1a**−**d** (Table 1). Additionally, the known *N*-Cbz L-proline[11] **2e** was prepared according to known methods. Initial attempts to perform the Blaise reaction on aminonitriles **2a**−**d** resulted in low yields and complex mixtures of products. It appeared that the presence of a secondary amino group was deleterious to the reaction, probably due to competitive deprotonation and alkylation. Therefore, a second protection of the nitrogen atom as a benzyl ether was envisaged. Thus, deprotonation of α-aminonitriles **2a**−**d** (NaH, DMF) and addition onto a solution of benzyl iodide gave the α-aminonitriles **3a**−**d** in good yields without racemization, as determined by HPLC. These special conditions were used to avoid racemization, as observed using standard benzylation conditions.

The Blaise reaction on aminonitriles **2e** and **3a**−**d** was accomplished by treatment with excess *tert*-butyl bromoacetate in the presence of zinc (activated with 1,2-dibromoethane) in refluxing THF, followed by quenching with 50% aqueous potassium carbonate. However, the expected enaminoesters **4a**−**e** were obtained as minor products,[12] the major being the 2-imidazolidinone derivatives **5a**−**e** (Scheme 1). These compounds result from intramolecular reaction of the intermediate iminozincate onto the benzyl carbamate. Actually, it was possible to transform the acyclic enaminoesters **4a**−**e** into the cyclic derivatives **5a**−**e** by treatment with NaH. This was routinely achieved after extraction to obtain pure **5a**−**e**.

Conditions for the Blaise reaction allow the products to be obtained in good yields. No substitution of the nitrile group by the enolate was observed. Moreover, all the enaminoesters **5a**−**e** were obtained as single diastereomers without any racemization, as determined by chiral HPLC.

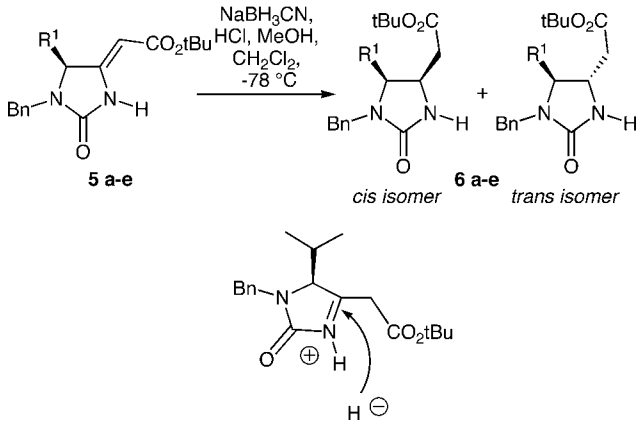
(6) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833.
(7) (a) Mauduit, M.; Kouklovsky, C.; Langlois, Y.; Riche, C. *Org. Lett.* **2000**, *2*, 1053. (b) Mauduit, M.; Kouklovsky, C.; Langlois, Y. *Eur. J. Org. Chem.* **2000**, 1595.
(8) Dondoni, A.; Massi, A.; Minghini, E. *Synlett* **2006**, 539.
(9) Blaise reaction with cyanohydrins: Syed, J.; Forster, S.; Effenberger, F. *Tetrahedron: Asymmetry* **1998**, *9*, 805.
(10) The whole synthetic sequence was performed on both racemic and enantiomerically pure material for each amino acid. The enantiomeric purity of each intermediate was checked by HPLC on a chiral column.
(11) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.
(12) Compounds **4a**−**e** were obtained as single diastereomers as always observed for the Blaise reaction: Lee, A. S.-Y.; Cheng, R.-Y.; Pan, O.-G. *Tetrahedron Lett.* **1997**, *38*, 443.

Scheme 1. Blaise Reaction of Protected α-Aminonitriles



The reduction of imidazolines **5a**−**e** was carried out under three different conditions: hydrogenation, hydride, or dissolving metal reductions. Hydrogenation at ambient pressure resulted in migration of the exocyclic double bond into the imidazolidone ring, thus inducing complete racemization. In contrast, low-temperature reduction with sodium cyanoborohydride in acidic medium gave good yields of the reduced compounds **6a**−**e** without loss of enantiomeric purity. Reduction of the valine derivative **5b** gave **6b** as a single diastereomer (Table 2, entry b), whereas reduction of other substrates gave a mixture of stereomers.[13] The relative configuration of **6b** was determined to be 1,2-cis by X-ray crystallography after removal of the benzyl group on nitrogen to give **7b** (Figure 3). The cis selective reduction of valine derivative **5b** is believed to proceed via an acyliminium species, in which the hydride attacks on the opposite face to the R^1 substituent (*si* face, Table 2).

Table 2. Diastereoselective Reduction of **5a**−**e** with Sodium Cyanoborohydride



entry	substrate	yield (%)	cis/trans[a]
a	**5a**	74	1.6:1
b	**5b**	84	>99:1
c	**5c**	55	1:2
d	**5d**	55	1:1.5
e	**5e**	67	1:2

[a] Ratio determined by ^{1}H NMR analysis of the crude product.

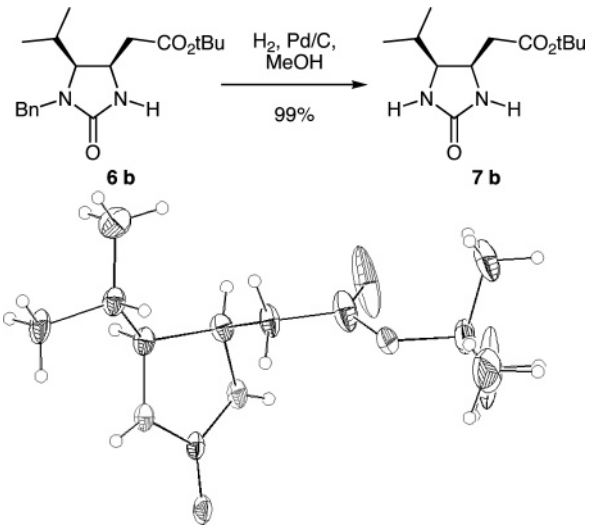


Figure 3. X-ray crystal of compound **7b**.

Reduction under dissolving metal conditions[14] was next attempted; treatment of cyclic enaminoesters **5a**−**e** with sodium in THF/ammonia[15] gave a mixture of reduced products consisting of the reduced ester, the corresponding carboxylic acid, and the primary alcohol.[16] For easier characterization, the crude mixture was treated with refluxing NaOH solution to give a mixture of the carboxylic acid **8a**−**d** and primary alcohol **9a**−**d** (Table 2). Importantly, both compounds were always obtained as *single diastereomers*. Reoxidation of primary alcohols **9a**−**d** (PDC, DMF) gave carboxylic acids **8a**−**d** with the same relative configuration, thus proving that the reduction is totally diastereoselective. A comparison between ^{1}H and ^{13}C NMR spectra of compound **8b** and the acid obtained after saponification of ester **6b** showed that the relative configuration obtained by reduction with Na/NH_3 was *different from that obtained by cyanoborohydride reduction*. To explain this stereoselectivity, we suggest that the reaction proceeds first via a radical anion intermediate which adopts the trans configuration owing to the stabilization of the SOMO orbital by the neighboring

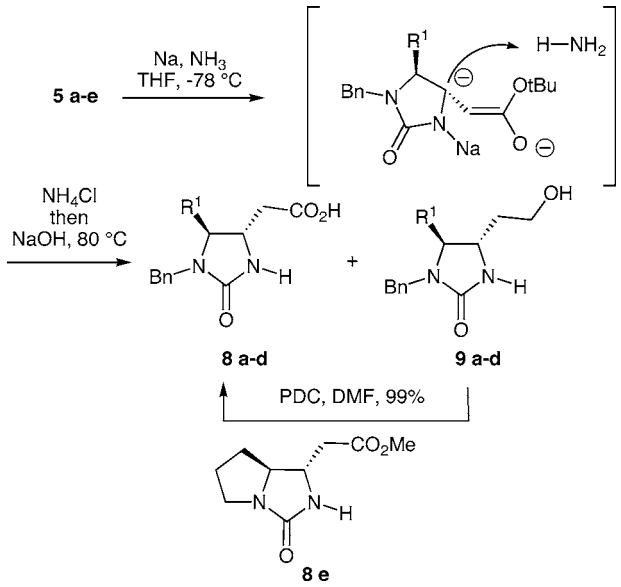
(13) Tetrabutylammonium cyanoborohydride or sodium triacetoxyborohydride did not improve the stereoselectivity.

(14) Reviews: (a) Venturello, P.; Barbero, M. *Science of Synthesis*; Georg Thieme Verlag: Stuttgart, 2005; Vol. 8b, p 881. (b) Caine, D. *Org. React. (New York)* **1976**, *23*, 1.

(15) To the best of our knowledge, there is only one example of reduction of an enaminoester derivative under Birch conditions: Schlessinger, R. H.; Iwanowicz, E. J.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 3070.

(16) The presence of alcohol **9a**−**d** must be due to traces of moisture in the reaction medium.

Table 3. Reduction of Enamines **5a**−**d** under Dissolving Metal Conditions



entry	substrate	yield of **8** (%)	yield of **9** (%)	de (%)
1	**5a**	52	27	>99
2	**5b**	50	23	>99
3	**5c**	47	15	>99
4	**5d**	50	18	>99
5	**5e**	44[a]	-	>99

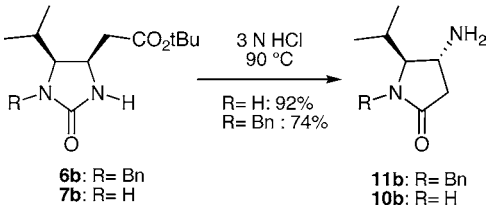
[a] Compound **8e** was isolated as its methyl ester.

C−C bond.[17] Further electron transfer gives an anionic intermediate which is protonated by ammonia from the β face (*re* face) to give 1,2-*trans*-imidazolidinone[18] (Table 3).

(17) For a discussion about the stereoselectivity of the Birch reduction: Pradhan, S. K. *Tetrahedron* **1986**, *42*, 6351.

(18) Similarity between ^{1}H and ^{13}C NMR spectra of compounds **8a**−**e** and minor isomers for compounds **6a** and **6e** allowed cis/trans assignment for each isomer in compounds **6a**−**e** (see Supporting Information for details).

Scheme 2. Synthesis of 4-Amino-pyrrolidinones **10b** and **11b**



Hydrolysis of the imidazolidine-2-one **7b** was accomplished by treatment with 3 N HCl at 90 °C, giving lactam **10b** as a single product after purification on Dowex resin. Alternatively, the N-benzylated γ-lactam **11b** could be obtained from **6b** by omitting the hydrogenolysis step (Scheme 2).

In conclusion, we have described a general and stereoselective entry into new functionalized 1,2-diamines from α-aminoacids using a chemoselective zinc-mediated homologation of α-aminonitriles, followed by a stereoselective reduction. The 4-aminopyrrolidinones obtained after hydrolytic cleavage of ureas might be transformed into β,γ-diaminoacids by saponification or into 3-aminopyrrolidines by reduction. These applications, as well as the total synthesis of structurally related natural products, are currently under study.

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Supporting Information Available: Experimental procedures and analytical and spectral characterization for all new compounds, including a CIF file with X-ray data for compound **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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