Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8655–8658

Asymmetric synthesis of α,β-substituted β-aminoalkanamides and stereochemical determination

Vito Capriati,[a] Leonardo Degennaro,[a] Saverio Florio,[a,*] Renzo Luisi[a] and Corrado Cuocci[b]

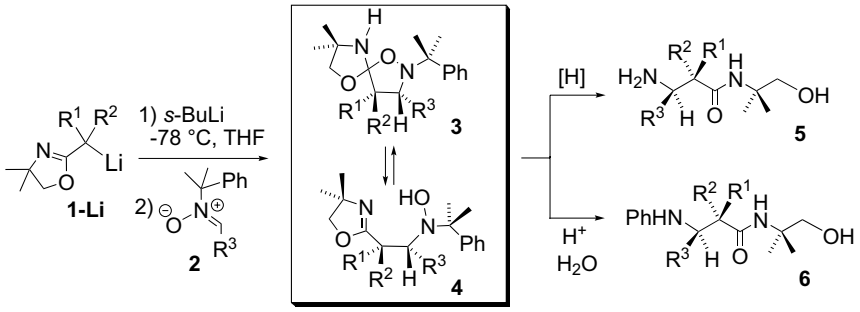
[a]*Dipartimento Farmaco-Chimico, Università di Bari, Consorzio Interuniversitario Nazionale CINMPIS, Via E. Orabona 4, I-70125 Bari, Italy*
[b]*Istituto di Cristallografia (IC-CNR), Via Amendola 122/o, I-70125 Bari, Italy*

Received 12 July 2007; revised 2 October 2007; accepted 5 October 2007
Available online 10 October 2007

Abstract—Highly enantiomerically enriched β-aminoalkanamides **12** and β-phenylaminoalkanamides **13** have been prepared by the addition reaction of α-lithiated 2-alkyl-2-oxazolines **9-Li**, derived from optically active oxazolines **9**, to *N*-cumyl nitrones **2**. The relative stereochemistry of alkanamides **5** and **6** has been established by 1D-NOESY experiments carried out on the related pyrimidinones **7**, whereas the absolute configuration of alkanamides **12** and **13** has been confirmed by an X-ray analysis.

In the preceding paper,[1] we described a highly diastereoselective preparation of β-aminoalkanamides **5** and β-phenylaminoalkanamides **6** based on the addition of α-lithiated 2-alkyl-2-oxazolines **1-Li** to *N*-cumyl nitrones **2** and subsequent reduction and hydrolysis, respectively (Scheme 1). The diastereoselectivity of the above addition, the relative configuration of the so formed alkanamides **5** and **6** as well as the preparation of the optically active β-aminoalkanamides and products that can be derived from, are reported and discussed in the present Letter.

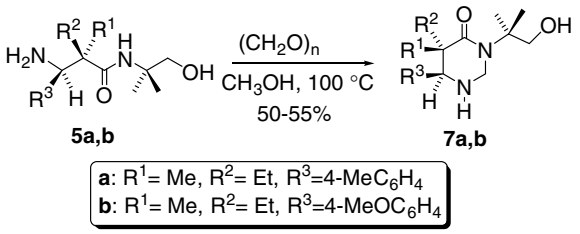
The stereochemistry of β-aminoalkanamides **5a**,**b**, prepared as described in the preceding paper, was established by detecting transient positive NOE effects (diagnostic of a spatially close protons relationship) after applying selective ^{1}H pre-irradiation within a double pulsed field gradient spin-echo (DPFSGE-NOE) sequence[2] on the corresponding hexahydro-4-pyrimidinone derivatives **7a**,**b**,[3] which have been prepared by cyclization of the β-aminoalkanamides **5a**,**b** with formaldehyde (Scheme 2).[4,5] Indeed, as shown in Figure 1, a pre-irradiation of H_A enhanced either the



Scheme 1. Synthesis of α,β-substituted-β-aminoalkanamides **5** and **6**.

Keywords: Oxazolines; Amino acids; Asymmetric synthesis; Lithiation; Nitrones.
* Corresponding author. Tel.: +39 0805442749; fax: +39 0805442539; e-mail: florio@farmchim.uniba.it

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.10.035



Scheme 2.

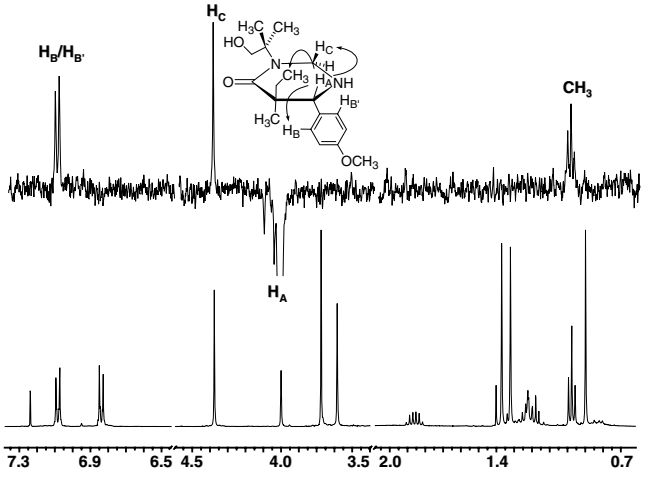


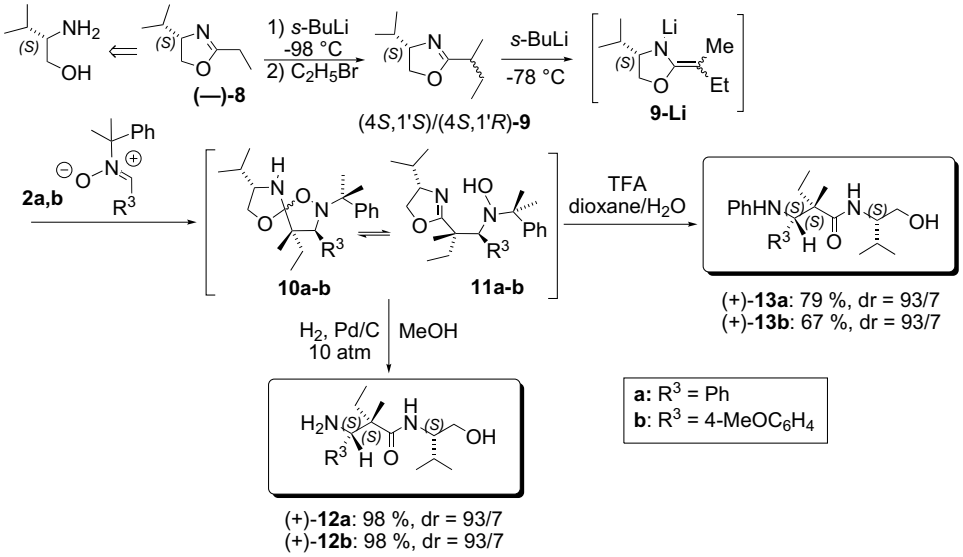
Figure 1.

$H_B/H_{B'}$ phenyl protons or the methyl ethyl protons, so supporting a R^*,R^* relative configuration for the pyrimidinones stereogenic centres whose stereochemistry should be consistent with that of the precursors β-aminoalkanamides **5a**,**b**. The assigned stereochemistry was also confirmed, in the case of **7b**, by an X-ray analysis run on the precursor alkanamide **5b**.

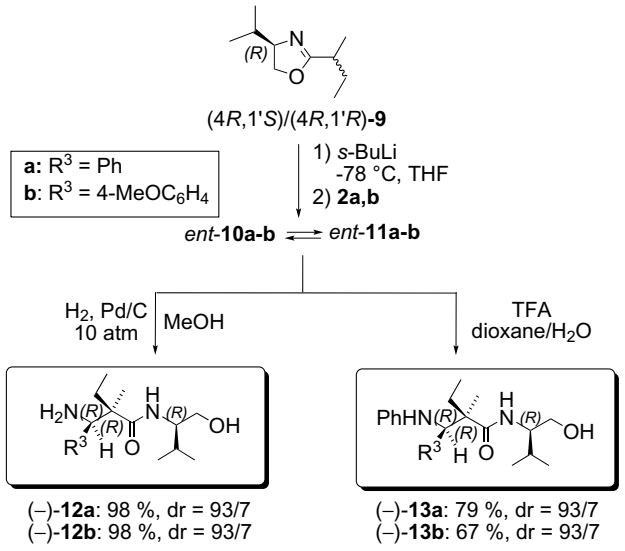
Considering the high diastereoselectivity of the addition reaction of lithiated 2-alkyl-2-oxazoline **1-Li** to nitrones, it was almost obvious at this stage that the chiral version of such a reaction had to be tested. We evaluated the possibility of performing an asymmetric synthesis of such aminoalkanamides simply starting from optically active alkyloxazolines (Scheme 3). (4*S*)-2-Ethyl-4-isopropyl-2-oxazoline (−)-**8** was prepared starting from L-valinol and triethylorthopropionate.[6] Ethylation of (−)-**8** (*s*-BuLi, THF, EtBr at −98 °C) gave an almost 1:1 diastereomeric mixture of the corresponding 2-*s*-butyl-2-oxazoline (4*S*,1′*S*)/(4*S*,1′*R*)-**9**. All attempts to separate such a diastereomeric mixture failed, so we decided to use it as such also in view of the fact that in the lithiation reaction of **9** the stereogenic centre in the α position is lost in the formation of the azaenolate **9-Li**.[7] Lithiation of (4*S*,1′*S*)/(4*S*,1′*R*)-**9** with *s*-BuLi, followed by the addition of nitrones **2a**,**b**, afforded the mixtures of equilibrating spirocyclic compounds **10a**,**b** and hydroxylamines **11a**,**b** in good yields (Scheme 3).[8]

Hydrogenation of the mixtures **10a/11a** and **10b/11b** (H_2, 10 atm, Pd/C, MeOH, 25 °C, 16 h) produced almost quantitative yields of β-aminoalkanamides (+)-**12a** and (+)-**12b** in a highly diastereo- and enantioselective manner (Scheme 3).[9] The same diastereo- and enantioselectivity was observed in the case of β-phenylaminoalkanamides (+)-**13a** and (+)-**13b** obtained upon hydrolysis of the mixtures **10** and **11** with trifluoroacetic acid (TFA) (Scheme 3).[10] As both these transformations did not involve the two new stereocenters, the diastereo- and enantioselectivity found in the final products **12** and **13** should also reflect that of **10** and **11**.

For the sake of comparison, the lithiation reaction of the enantiomeric oxazoline (4*R*,1′*S*)/(4*R*,1′*R*)-**9**, prepared starting from D-valinol, was evaluated. Deprotonation of (4*R*,1′*S*)/(4*R*,1′*R*)-**9** with *s*-BuLi and trapping with nitrones **2a**,**b** led to the formation of the equilibrating mixtures of spirocyclic compounds *ent*-**10a**,**b** and hydroxylamines *ent*-**11a**,**b** (Scheme 4).



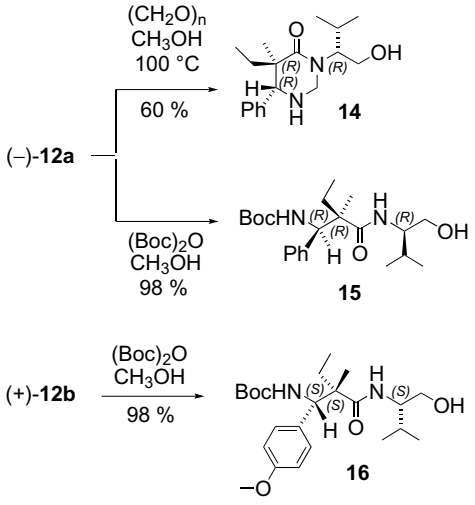
Scheme 3. Synthesis of chiral nonracemic spirocyclic compounds **10** in equilibrium with their hydroxylamine derivatives **11**, and their transformation into β-amino and β-phenylaminohydroxyamides **12** and **13**.



Scheme 4.

Hydrogenation of such mixtures (H_2, 10 atm, Pd/C, MeOH, 25 °C, 16 h) produced almost quantitative yields of β-aminoalkanamides (−)-**12a** and (−)-**12b** in a diastereo- and enantioselective manner. The same diastereo- and enantioselectivity was observed in the case of β-phenylaminoalkanamides (−)-**13a** and (−)-**13b** upon hydrolysis of *ent*-**10** and *ent*-**11** with TFA (Scheme 4).

To unequivocally establish the absolute configuration of alkanamides **12** and **13**, attempts were made to obtain crystalline derivatives to be subjected to an X-ray analysis. After several unsuccessful experimentations carried out on Boc-protected alkanamides **15** and **16** [derived from (4*R*)-2-ethyl-4-isopropyl-2-oxazoline (−)-**8** and its enantiomer (4*S*)-2-ethyl-4-isopropyl-2-oxazoline (+)-**8**, respectively] (Scheme 5) as well as on the tetrahydropyrimidinone **14**, prepared from (−)-**12a**, a crystalline product was obtained for *N*-phenylalkanamide (+)-**13a** after chromatographic separation from the minor diastereoisomer and re-crystallization (hexane/Et_2O 2:1, 73% overall yield). The X-ray analysis demonstrated

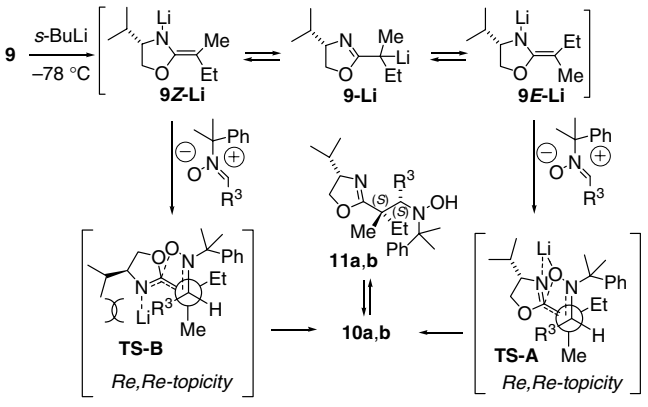


Scheme 5.

that it has the *S*,*S*,*S* configuration. By analogy, the alkanamide (−)-**12a**,**b** and (−)-**13a**,**b** should have the *R*,*R*,*R* configuration.

The overall stereoselectivity of this type of reactions, involving α-lithiated oxazolines, depends on the stereoselectivity in both the deprotonation and electrophilic substitution steps, as reported.[11] The α-deprotonation-alkylation of the chiral nonracemic oxazoline (−)-**8** resulted to be not stereoselective giving rise to **9** as a mixture of diastereoisomers; most probably, the subsequent deprotonation of **9** may also form a mixture of two diasteromeric azaenolates (**9*Z*-Li** and **9*E*-Li**). The reaction with nitrones, as a whole, being highly stereoselective, the electrophilic substitution step should be the crucial factor. To rationalize, for example, the *S*,*S* stereochemistry found in (+)-**12** and (+)-**13**, in the absence of a strong coordinating group for lithium on the oxazoline moiety and on the side chain,[11,7] it is plausible to assume that the two azaenolates, **9*Z*-Li** and **9*E*-Li**, equilibrate each other through the iminic carbanionic form **9-Li** (Scheme 6). In principle, each azaenolate could react with the nitrone according to four steric-approach descriptor pairs with reference only to the two new stereocenters found in the final products such as **12** and **13**: *Re*,*Re*, *Si*,*Si*, *Re*,*Si* and *Si*,*Re*. In this context, the successful (*Re*,*Re*)-approach between the azaenolate **9*E*-Li** and the *Z*-nitrone, that gives rise to the correct stereochemistry, is that taking place through the highly ordered transition state **TS-A**, which is more favoured above all either for steric reasons or for the fact of benefiting a double coordination of lithium from the oxazoline nitrogen and the nitrone oxygen (Scheme 6). On the other hand, the transition state **TS-B**, also leading to the same stereochemistry from the azaenolate **9*Z*-Li**, should be, from a steric point of view, less favoured with respect to **TS-A**; moreover, in this case, the above double coordination of lithium is lacking as well.

In conclusion, an asymmetric synthesis of β-amino and β-phenylaminoalkanamides, that are β-amino acid derivatives and can be transformed into dipeptide analogs, has been developed. The cyclization of **5** with formaldehyde afforded substituted hexahydro-4-pyrimidinones **7**, which might be used as reagents and have



Scheme 6.

also a potential as chiral auxiliaries in asymmetric synthesis.[3]

Acknowledgements

This work was carried out under the framework of the National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni' and financially supported by MIUR and the University of Bari.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.035.

References and notes

1. Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R. *Tetrahedron Lett.* **2007**, *48*, doi:10.1016/j.tetlet.2007.10.032.
2. Neuhaus, D.; Williamson, M. In *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989; p 264.
3. (a) Beaulieu, F.; Arora, J.; Veith, V.; Taylor, N.; Chapell, B. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 8727–8728; (b) Chu, K. S.; Konopelski, J. P. *Tetrahedron* **1993**, *49*, 9183–9190.
4. (a) Hajji, C.; Testa, M. L.; Zaballos-García, E.; Zaragozá, R. J.; Server-Carrió, J.; Sepúlveda-Arques, J. *Tetrahedron* **2002**, *58*, 3281–3285; (b) Lázár, L.; Lakatos, A. G.; Fúlop, F.; Bérnath, G.; Riddell, F. G. *Tetrahedron* **1997**, *53*, 1081–1088; (c) Melon, D.; Gravier-Pelletier, C.; Le Merrer, Y.; Depezay, J. C. *Bull. Chem. Soc. Fr.* **1992**, *129*, 585–593.
5. *General procedure for the preparation of hexahydro-4-pyrimidinones* **7a**,**b**: A solution of **5a** (0.1 mmol, 31 mg) in MeOH (5.0 mL) and paraformaldehyde (10 mg) was heated in a sealed reactor at 100 °C for 8 h. The solvent was evaporated and the crude mixture was purified by flash chromatography (CH_2Cl_2/MeOH 9:1).
6. Kamata, K.; Agata, I.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 3113–3116.
7. Abbotto, A.; Bradamante, S.; Florio, S.; Capriati, V. *J. Org. Chem.* **1997**, *62*, 8937–8940.
8. *Typical procedure for the preparation of equilibrating mixtures of spirocyclic compounds* **10** *and hydroxylamines* **11**: To a pre-cooled (−78 °C, dry ice/acetone bath) solution of alkyloxazoline **9** (1.2 mmol) in 10 mL of THF under N_2 was added *s*-BuLi (solution in cyclohexane 1.4 M, 1.2 mmol). The resulting orange mixture was stirred for 20 min at this temperature before adding slowly a solution of the nitrone **2a** (THF, 5 mL, 1.0 mmol). Then, the reaction mixture was warmed up to room temperature, quenched with satd aq NH_4Cl, poured into 20.0 mL of saturated brine, extracted with Et_2O (3×10 mL), dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude mixture was flash-chromatographed (silica gel; petroleum ether/AcOEt = 7–8:3–2) to give a mixture of *N*-cumyl-1,6-dioxa-4,7-diazaspiro[4,4]nonanes **10** and corresponding *N*-cumyl-hydroxylamine **11**.
9. *General procedure for the preparation of 3-aminoalkanamides* **12**: To a solution of equilibrating mixture of **10** and **11** (0.5 mmol) in MeOH (5.0 mL) Pd/C (10% mol) was added and the resulting mixture was hydrogenated in a 'Büchi Mini Clave' apparatus at 10 bar overnight. Then, the solution was filtered on a Celite pad and the solvent evaporated *in vacuo* affording the 3-aminoalkanamides (**12**) that did not need further purification.
10. *General procedure for the preparation of* β*-phenylaminoalkanamides* **13**: To an equilibrating mixture of the spirocyclic compound **10** and hydroxylamine **11** (0.3 mmol) in dioxane/H_2O (4:1, 5 mL) CF_3COOH (20 μL) was added and the resulting mixture stirred for 24 h at rt. After this time, the reaction mixture was poured into water, extracted with AcOEt (3×10 mL), dried on Na_2SO_4, filtered and the volatiles were removed under reduced pressure. Column chromatography (AcOEt/petroleum ether, 1:4) furnished the phenylaminoalkanamides **13**.
11. (a) Hoobler, M. A.; Bergbreiter, D. A.; Newcomb, M. *J. Am. Chem. Soc.* **1978**, *100*, 8182; (b) Meyers, A. I.; Snyder, E. S.; Ackerman, J. J. H. *J. Am. Chem. Soc.* **1978**, *100*, 8186.