Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8651–8654

Oxazoline-mediated highly stereoselective synthesis of α,β-substituted-β-aminoalkanamides, potential precursors of unnatural $\beta^{2,2,3}$-amino acids

Vito Capriati, Leonardo Degennaro, Saverio Florio* and Renzo Luisi

Dipartimento Farmaco-Chimico, Università di Bari and Consorzio Interuniversitario Nazionale CINMPIS, Via E. Orabona 4, I-70125 Bari, Italy

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

Dedicated to Professor Miguel Yus of the University of Alicante in occasion of his 60th birthday

Abstract—The reaction of α-lithiated-2-alkyl-2-oxazolines **1-Li** with aliphatic, aromatic and heteroaromatic *N*-cumyl nitrones results in the stereoselective formation of *N*-cumyl-1,6-dioxa-2,9-diazaspiro[4,4]nonanes **3** which equilibrate with the hydroxylamino derivatives **4**. Such equilibrating mixtures can be easily transformed into β-amino alkanamides **5** under reductive conditions, whereas acidic hydrolysis with trifluoroacetic acid (TFA) furnishes high yields of β-phenylamino alkanamides **6** via a cumene hydroperoxide-type rearrangement. Derivatives **5** and **6** provide a backbone of potentially useful unnatural $\beta^{2,2,3}$-amino acids.

Nucleophilic addition of oxazolinyl- and aryloxiranyllithiums to nitrones proved to be a useful methodology for the preparation of a new class of unnatural β-amino acids,[1] α-epoxy-β-amino acids,[2] α,β-epoxy-γ-amino acids,[3] [1,2]oxazetidines,[4,5] and new molecular scaffolds.[6] A drawback of this methodology is the removal of the N-protecting group (deriving from the nitrone) in the final product. In the present Letter we report on the addition of α-lithiated 2-alkyl-2-oxazolines to *N*-cumyl nitrones, which allow the preparation of new functionalized compounds. The selection of *N*-cumyl nitrones was suggested by the observation that *N*-cumyl substituted-γ-amino acids can be easily N-deprotected.[3]

Treatment of lithiated 2-methyloxazoline **1a-Li**, generated by lithiation of **1a** (*s*-BuLi, THF, −78 °C, 15 min),[7] with *N*-cumylnitrone **2a**,[8,9] followed by an acidic quenching, resulted in the formation of an equilibrating mixture of *N*-cumyl-1,6-dioxa-2,9-diazaspiro[4,4]nonane **3a** and the hydroxylamine derivative **4a**, as ascertained by an IR and ^{1}H, ^{13}C NMR inspection.[10]

Similarly, the reaction of lithiated **1b–d-Li** with aliphatic, aromatic and heteroaromatic *N*-cumyl nitrones **2b–g** furnished mixtures of **3b–l** and **4b–l** in good to excellent yields (Table 1).

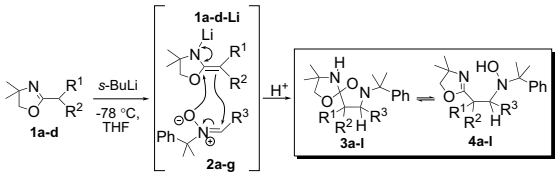
The formation of compounds **3** and **4**, accordingly to a reported mechanism,[6] could be reasonably accounted for with the nucleophilic addition of **1-Li** to the C=N double bond of nitrone **2** followed by the nucleophilic attack of the hydroxylaminolate intermediate to the C=N double bond of the oxazoline moiety (Table 1).

Unfortunately, the equilibrium established in the solution between **3** and **4** made difficult any estimation of the stereoselectivity of the reaction of lithiated oxazolines **1b-Li** and **1d-Li** either by NMR or other analytical techniques (GC, HPLC). To get insight on the stereoselectivity, the mixtures of **3** and **4** were subjected to transformations that did not involve the newly created stereogenic centres (with the exception of the *spiro* carbon). Indeed, hydrogenation (H_2, 10 atm, Pd/C, MeOH, 25 °C, 16 h)[3] carried out on the mixtures of **3/4** resulted in simultaneous cumyl group removal and N–O bond cleavage giving β-amino alkanamides **5a–i** in high yield and high diastereoselectivity in the case of the conversion of **3f–l/4f–l** to **5d–i** (Table 2).[11]

Keywords: Oxazolines; Amino acids; Peptides; 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.2007.10.032

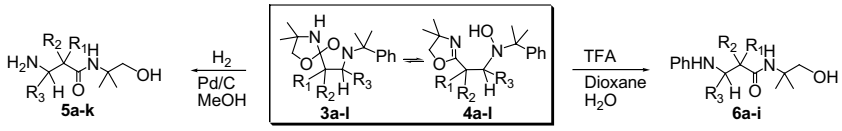
Table 1. Reaction of α-lithiated oxazolines **1a–d-Li** with nitrones **2a–g**



Oxazoline **1**	R^1	R^2	Nitrone **2**	R^3	Mixture **3/4**	Yield[a,b] (%)
1a	H	H	**2a**	*p*-MeC_6H_4	**3a/4a**	60[c]
1b	H	CH_3	**2b**	C_6H_5	**3b/4b**	93
1b	H	CH_3	**2a**	*p*-MeC_6H_4	**3c/4c**	72
1c	CH_3	CH_3	**2b**	C_6H_5	**3d/4d**	50
1c	″	″	**2c**	*p*-ClC_6H_4	**3e/4e**	93
1d	C_2H_5	CH_3	**2b**	C_6H_5	**3f/4f**	96
″	″	″	**2a**	*p*-MeC_6H_4	**3g/4g**	89
″	″	″	**2c**	*p*-ClC_6H_4	**3h/4h**	66
″	″	″	**2d**	*p*-$MeOC_6H_4$	**3i/4i**	58
″	″	″	**2e**	2-Furyl	**3j/4j**	67
″	″	″	**2f**	C_6H_{11}	**3k/4k**	67
″	″	″	**2g**	$CH_3(CH_2)_6$	**3l/4l**	59

[a] An inseparable mixture of equilibrating spirocyclic and hydroxylamino forms was always obtained.
[b] Isolated yields after flash column chromatography.
[c] Oxazolinylstyrene was also isolated (see Ref. 6).

Table 2. Preparation of β-aminoalkanamides **5** and β-phenylaminoalkanamides **6**



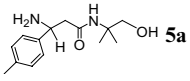
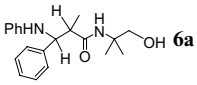
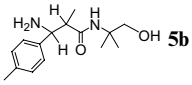
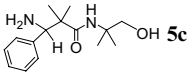
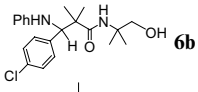
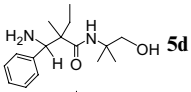
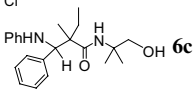
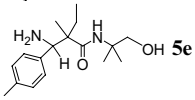
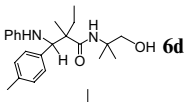
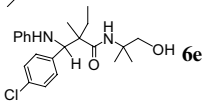
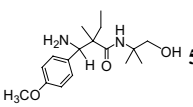
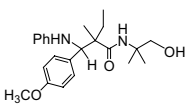
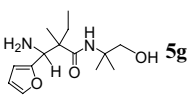
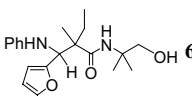
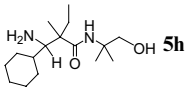
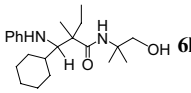
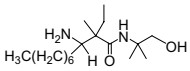
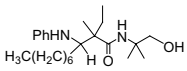
Mixture **3/4**	β-Aminoalkanamide **5**	Yield[a] (%)	β-Phenylaminoalkanamide **6**	Yield[a] (%)	dr[b]
3a/4a	 **5a**	98	—[c]	—	—
3b/4b	—	—	 **6a**	68	70:30[d]
3c/4c	 **5b**	98	—	—	70:30[d]
3d/4d	 **5c**	″	—	—	—
3e/4e[a]	″	″	 **6b**	85	—
3f/4f	 **5d**	″	 **6c**	72	94:6
3g/4g	 **5e**	″	 **6d**	70	95:5
3h/4h[a]	**5d**	″	 **6e**	82	95:5
3i/4i[b]	 **5f**	″	 **6f**	60[b]	89:11[d]
3j/4j	 **5g**	″	 **6g**	67	94:6

Table 2 (*continued*)

Mixture **3/4**	β-Aminoalkanamide **5**	Yield[a] (%)	β-Phenylaminoalkanamide **6**	Yield[a] (%)	dr[b]
3k/4k	 **5h**	〃	 **6h**	76	94:6
3l/4l	 **5i**	〃[e]	 **6i**	68	92:8

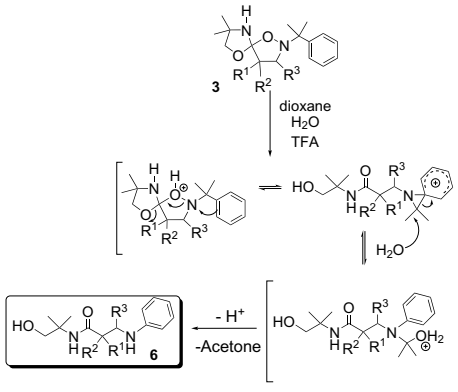
[a] Isolated yield.
[b] Diastereomeric ratio (dr) calculated by ^{1}H NMR analysis on the crude reaction mixtures. The same dr has been always found for both transformations.
[c] Under acidic conditions, an elimination reaction occurs and the corresponding oxazolinylstyrene has been isolated (see Ref. 6).
[d] Separable mixture of diastereomers (silica gel, petroleum ether/AcOEt).
[e] Compound spectroscopically characterized as *N*-Boc derivative.

It is worth noting that the structure of an unnatural $\beta^{2,2,3}$-amino acid (according to Seebach's definition) is embedded in the backbone of the β-amino alkanamides **5a–i**, a kind of substances which are not easy to obtain and that could be of interest either from a biological or a structural point of view.[12]

As reported, when a mixture of **3a/4a** was treated with silica gel or with TFA in dioxane/H_2O at rt for 24 h, a stereoselective elimination of cumylhydroxylamine took place giving oxazolinylstyrene (95% yield; trans/cis ratio >99:1) as the main product.[6] In contrast, when a mixture of **3b/4b** was treated with TFA, under the same experimental conditions a different transformation occurred leading in a good yield and reasonable diastereoselectivity to the β-phenylamino hydroxyalkylamide **6a** (Table 2). Similarly, the mixtures **3e–l/4e–l** were converted into β-phenylaminoamides **6b–i** upon hydrolysis with TFA or Amberlist-15 (Table 2).[13] Conversion of mixtures **3/4** into **6** might be explained with a cumene hydroperoxide-type rearrangement[14,15] involving a phenonium ion resulting from the C to N phenyl migration simultaneously to the TFA-promoted N–O bond cleavage of **3**. Then, the phenonium ion would be attacked by H_2O ending up with the formation of the β-amino amide **6** (Scheme 1).

Once more, the conversion of the mixtures of **3f–l/4f–l** to **6c–i** was highly diastereoselective (Table 2).

The results obtained clearly demonstrate that the reaction of **1d-Li** ($R^1 = C_2H_5$, $R^2 = CH_3$) with nitrones is highly stereoselective, according to what is reported for other lithiated oxazolines;[1–4,6] the slightly lower diastereoselectivity (dr: 70:30, Table 2) observed in the reaction of lithiated oxazoline **1b-Li** ($R^1 = H$, $R^2 = CH_3$) likely could be the result of a substituent effect on the lithiated carbon.



Scheme 1. Rearrangement of **3** to **6**.

In conclusion, in this Letter we report a very simple and efficient preparation of β-amino- and β-phenylamino alkanamides (potential precursors of $\beta^{2,2,3}$-amino acids)[16] based on the addition of α-lithiated-2-alkyl-2-oxazolines to cumyl nitrones followed by reduction and hydrolysis, respectively. The usefulness of the cumyl group that can be easily introduced and removed under different reaction conditions is remarkable. The chiral version of the above synthetic procedure leading to optically active β-amino- and β-phenylamino alkanamides is described in the following paper.

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.2007.10.032.

References and notes

1. Luisi, R.; Capriati, V.; Florio, S.; Vista, T. *J. Org. Chem.* **2003**, *68*, 9861–9864.
2. Luisi, R.; Capriati, V.; Degennaro, L.; Florio, S. *Org. Lett.* **2003**, *5*, 2723–2726.
3. Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Punzi, P. *Org. Lett.* **2006**, *8*, 4803–4806.
4. Luisi, R.; Capriati, V.; Florio, S.; Piccolo, E. *J. Org. Chem.* **2003**, *68*, 10187–10190.
5. Capriati, V.; Florio, S.; Luisi, R.; Salomone, A.; Cuocci, C. *Org. Lett.* **2006**, *8*, 3923–3926.

6. Capriati, V.; Degennaro, L.; Florio, S.; Luisi, L. *Eur. J. Org. Chem.* **2002**, 2961–2969.
7. *Typical procedure for the preparation of spirocyclic compounds* **3a–l** *and hydroxylamines* **4a–l**: To a pre-cooled (−78 °C) solution of alkyloxazoline **1a–d** (1.2 mmol) in 10 mL of THF under N_2, *s*-BuLi was added (1.4 M cyclohexane solution, 1.2 mmol). The resulting orange mixture was stirred for 20 min at this temperature and a solution of nitrone **2a–g** (THF, 5 mL, 1.0 mmol) was added dropwise. The reaction mixture was warmed up to rt, quenched with satd aq NH_4Cl, poured into 20 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 = 8–9:2–1) to give the *N*-cumyl-1,6-dioxa-4,7-diazaspiro[4,4]nonanes **3a–l** equilibrating with the corresponding *N*-hydroxy-*N*-cumyl-2-(oxazolin-2-yl)-alkanamides **4a–l**.
8. Gautheron-Chapoulaud, V.; Pandya, S. U.; Cividino, P.; Masson, G.; Py, S.; Vallée, Y. *Synlett* **2001**, 1281–1283.
9. Franco, S.; Merchán, F. L.; Merino, P.; Tejero, T. *Synth. Comm.* **1995**, *25*, 2275.
10. All attempts to separate spirocyclic derivatives **3** in a pure form failed so far and, in all cases, equilibrating mixtures of **3** and **4** were always obtained. In the solution, spirocyclic compounds **3** equilibrate with the corresponding hydroxylamino forms **4** with the position of the equilibrium being dependent upon the nature of the nitrone and oxazoline substituents (R^1, R^2, R^3); indeed, the hydroxylamino form **4** is mainly present with aliphatic nitrones and oxazolines **1a**,**b**,**d**, whereas the spirocyclic form **3** represents the main compound in the case of aromatic nitrones and oxazoline **1c**. By ^{13}C NMR spectroscopy, spirocyclic forms **3** (C_{spiro} ca. 120 ppm) may be distinguished from hydroxylamino forms **4** (C=N ca. 160 ppm).
11. The relative stereochemistry to compounds **5** and **6** has been determined by NMR experiments and confirmed by an X-ray analysis (see doi:10.1016/j.tetlet.2007.10.035).
12. For an extensive review on β- and γ-amino acids and peptides, see: Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111–1239.
13. *General procedure for the preparation of phenylaminopropanamides* **6a–i**: To a mixture of the spirocyclic compound **3b–l** and hydroxylamine **4b–l** (0.3 mmol) in dioxane/H_2O (4:1, 5 mL) TFA (20 μL) was added and the resulting mixture stirred for additional 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 phenylamino alkanamides **6a–i**.
14. (a) Hamann, H. J.; Liebscher, Y. *J. Org. Chem.* **2000**, *65*, 1873–1876; (b) Kabalka, W. G.; Reddy Kesavulu, N.; Narayana, C. *Tetrahedron Lett.* **1993**, *34*, 7667–7668.
15. An anionic carbon to nitrogen phenyl migration has been also reported: Theodorou, V.; Skobridis, K.; Karkatsoulis, A. *Tetrahedron* **2007**, *63*, 4284–4289.
16. Examples of biological activity of β-amino acid derivatives have been reported; see: (a) Audia, J. E.; Porter, W. J.; Scott, W. L.; Stack, D. R.; Thompson, R. C. Patent WO 01/34571 A1, 2001; *Chem. Abstr.* **2001**, *134*, 367191; (b) Camaggi, G.; Filippini, L.; Gusmeroli, M.; Mormile, S.; Signorini, E.; Garavaglia, C. Patent EP 0718280 A2, 1996; *Chem. Abstr.* **1996**, *125*, 168644.