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New Synthesis of Optically Active 5-Isoxazolidinones and β-Amino Acids

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Abstract: A new simple and stereoselective synthesis of 5-isoxazolidinones based on the reaction of lithiated 2-isopropyl-2-oxazolines with nitrones is described. A chiral version of such a methodology allows the preparation of highly enantioenriched 5-isoxazolidinones which are useful precursors for the synthesis of β-amino acids

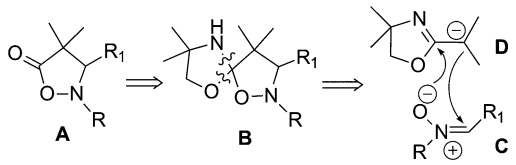
Isoxazolidinones are well-established building blocks in synthetic organic chemistry. Synthetic routes to them are numerous, including the enantioselective conjugate addition of hydroxylamines to pyrazolidinone acrylamides,[1] propenoates,[2] crotonic acid esters,[3] and α,β-unsaturated-δ-lactones.[4] The 1,3-dipolar cycloaddition of nitrones with ynolates to give isoxazolidinones has been developed quite recently.[5]

One of the reasons the isoxazolidinones, particularly 5-isoxazolidinones, are of considerable interest to organic chemists is that they are good precursors to unnatural β-amino acids: these are, indeed, unmasked forms of 5-isoxazolidinones.

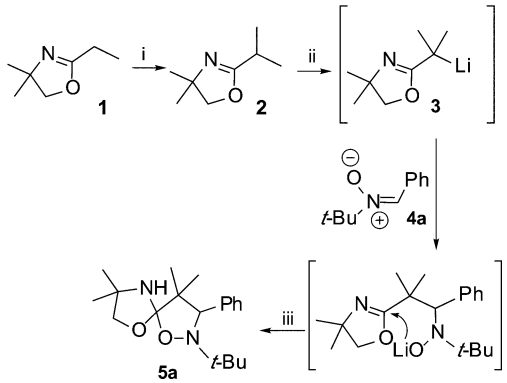
In a research project focused on the development of new methodologies based on the use of metalated 2-alkyl-2-oxazolines we envisaged that 5-isoxazolidinones could be achieved from 2-alkyl-2-oxazolines according to the retrosynthetic approach shown in Scheme 1, where the 5-isoxazolidinone system **A** is seen as obtainable by hydrolysis of the spirocyclic oxazolidinylisoxazolidine **B** which derives from the reaction of the nitrone **C** with 2-alkyl-2-oxazoline **D** (Scheme 1).

In this paper, we report a novel and stereoselective synthesis of 5-isoxazolidinones based on the reaction of 2-isopropyl-2-oxazolines with nitrones. In previous papers, concerned with the reaction of lithiated 2-alkyl-2-oxazolines with nitrones we demonstrated that spirocyclic oxazolidinylisoxazolidines are stable intermediates that can be isolated and eventually transformed into 2-alkenyl-2-oxazolines, oxazolinyl[1,2]oxazetidines, or 5-isoxazolidinones depending upon the experimental conditions.[6]

SCHEME 1



SCHEME 2[a]



[a] Key: (i) (a) LDA, −78 °C, THF, (b) CH_3I; (ii) *s*-BuLi/TMEDA, −78 °C, THF, 1 h; (iii) H^+.

Lithiation (*s*-BuLi/TMEDA, THF, −78 °C) of 2-isopropyl-4,4-dimethyl-2-oxazoline **2**, simply prepared from 2-ethyl-4,4-dimethyl-2-oxazoline **1** by the deprotonation−methylation sequence, furnished lithiated oxazoline **3**; the addition of nitrone **4a** after 1 h and workup with saturated aqueous NH_4Cl yielded the spiro[4,4]-1,6-dioxa-2,9-diazanonane **5a** highly diastereoselectively (dr > 98/2) (Scheme 2).

The formation of **5a** can be accounted for by assuming a nucleophilic addition of lithiated oxazoline **3** to the nitrone **4a** followed by a stereoselective addition of the resulting lithiated hydroxylamine to the C−N double bond of the oxazoline ring. The spirocyclic structure of **5a** was established by NMR and IR spectroscopy: the ^{13}C NMR spectrum showed the presence of the diagnostic resonance of the spiro carbon atom at 120 ppm and the absence of the C=N carbon of the oxazoline ring at 160 ppm. Moreover, the FT-IR analysis revealed a sharp absorption band at 3350 cm^{-1} (NH stretching) and the absence of the 1650 cm^{-1} band which is diagnostic for the oxazoline C=N bond. Equally highly stereoselective were the reactions with aryl nitrones **4b** and **4c** (Table 1) which afforded in good yields spirocyclic compounds **5b** and **5c**, respectively. Lower chemical yields of spirocyclic compounds **5d** and **5e** were obtained when we used aliphatic nitrones **4d** and **4e**: the diastereoselectivity was, however, once more very high.[7] To our satisfaction, the acidic hydrolysis of all the spirocyclic compounds **5a**−**e** with oxalic acid or trifluoroacetic acid (see the Supporting Information) furnished high to quantitative

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(1) Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181−4184.
(2) Baldwin, J. E.; Harwood, L. M.; Lombard, M. J. *Tetrahedron* **1984**, *40*, 4363−4370.
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(4) Panfil, I.; Maciejewski, S.; Belzecki, C.; Chmielewski, M. *Tetrahedron Lett.* **1989**, *30*, 1527−1528.
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(6) (a) Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R. *Tetrahedron Lett.* **2001**, *42*, 9183−9186. (b) Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R. *Eur. J. Org. Chem.* **2002**, 2961−2969.

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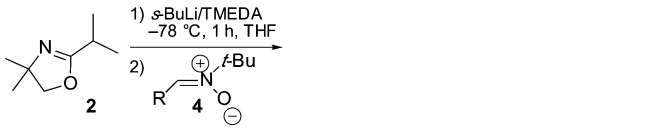
TABLE 1. Preparation of Spirocyclic Compounds 5,5-isoxazolidinones 6 and β-Amino Acids 7



R	nitrone **4**	spirocyclic compd **5** (% yield)[a,b]	5-isoxazolidinone **6** (% yield)[a]	β-amino acid **7** (% yield)
Ph	**4a**	**5a** (70)	**6a** (78)	**7a** (>98)
p-ClC_6H_4	**4b**	**5b** (74)	**6b** (>98)	**7a**·HCl (>98)[c]
p-$MeOC_6H_4$	**4c**	**5c** (72)	**6c** (34)	**7b** (>98)
Cy	**4d**	**5d** (38)[d]	**6d** (80)	**7c** (>98)
$CH_3(CH_2)_6$	**4e**	**5e** (35)[d]	**6e** (>98)	**7d** (>98)

[a] Isolated yields after column chromatography. [b] For all spirocyclic compounds **5** dr > 98/2. [c] The chlorine atom was lost in the course of reduction of **6b** and amino acid **7a** was obtained as a hydrochloride salt. [d] The spirocyclic compounds **5d,e** in solution equilibrate to the corresponding hydroxylamino forms (see ref 7).

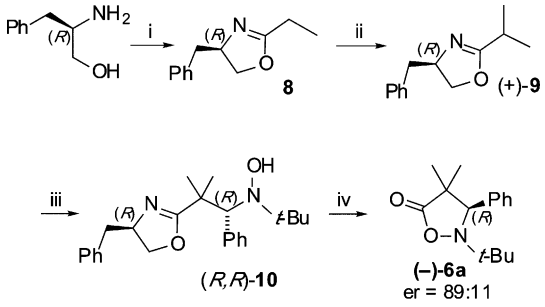
yields of isoxazolidin-5-ones **6a**−**e** (with the exception of **6c**), which are likely candidates for the elaboration to α- and β-substituted β-amino acids upon the N−O bond reduction. Indeed, treatment of **6a**−**e** with H_2 and Pd/C gave a quantitative yield of the β-amino acids **7a**−**d**.[8]

The asymmetric version of the above reaction starting from a chiral oxazoline came to our mind most obviously. The (4*R*)-2-ethyl-4-benzyl-2-oxazoline **8** was prepared from (*R*)-(+)-2-amino-3-phenyl-1-propanol and triethyl orthopropionate.[9] Lithiation of **8** with LDA followed by trapping with MeI produced a 75% yield of (4*R*)-(+)-2-isopropyl-4-benzyl-2-oxazoline **9**. Lithiation of (+)-**9** (*s*-BuLi/TMEDA, −78 °C, THF) followed after 1 h by the addition of nitrone **4a** gave the hydroxylamine (*R*,*R*)-**10** (71%) highly diastereoselectively (dr 90/10), as ascertained by ^{1}H NMR analysis. Treatment of (*R*,*R*)-**10** with oxalic acid gave the 5-isoxazolidinone (−)-**6a** (78% yield) with only an acceptable optical purity (er 89/11) (Scheme 3).[10]

So we decided to turn to another chiral oxazoline. The (4*R*)-2,4-diisopropyl-2-oxazoline (+)-**11** was synthesized from D-valinol using the same procedure followed for the preparation of oxazolines **2** and (+)-**9**. Lithiation of (+)-**11** and trapping with nitrone **4a** afforded the spirocyclic compound (*R*,*R*,*R*)-**12a** (R = Ph), in good yield (79%) and very high diastereoselectivity (dr 95/5), rapidly equilibrating in solution ($CDCl_3$) with its open hydroxylamino form (*R*,*R*)-**13a** (Scheme 4), as clearly indicated by an ^{1}H and ^{13}C NMR examination (see the Supporting Information). By crystallization from hexane only compound (*R*,*R*,*R*)-**12a** was found to be present in the solid state, as ascertained by the FT-IR spectrum run in KBr showing the absence of the C=N absorption band at 1660 cm^{-1} but the presence of the NH stretching at 3370 cm^{-1}; on the contrary, the FT-IR spectrum run in solution displayed the characteristic C=N absorption band of the oxazoline system together with the OH and NH stretching bands. The absolute configuration of (*R*,*R*,*R*)-**12a** was also unambiguously determined by means of a single-crystal X-ray analysis.[11]

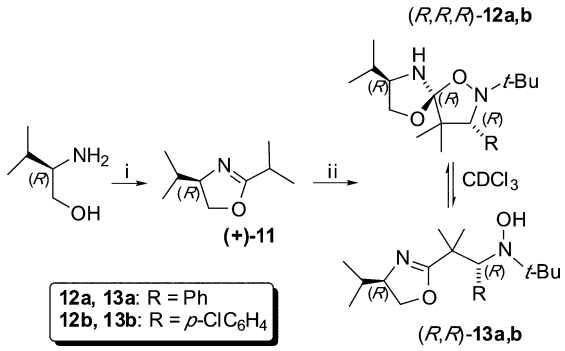
We did not care too much, however, about this equilibration simply because two of three stereogenic centers of (*R*,*R*,*R*)-**12a** were going to be lost in its hydrolysis to the corresponding 5-isoxazolidinone. Indeed, hydrolysis of (*R*,*R*,*R*)-**12a** in acidic conditions (CF_3COOH, dioxane/H_2O) furnished the isoxazolidinone (−)-**6a** highly enantioselectively (er 95/5) (Scheme 5).[12] This proves that the spirocyclic species are involved in the reaction leading to the 5-isoxazolidinone. Similarly, 5-isoxazolidinone (−)-

SCHEME 3[a]



[a] Key: (i) (a) $C_2H_5C(OEt)_3$, $(CH_2)_2Cl_2$, 70 °C; (ii) (a) LDA, −78 °C, THF, (b) CH_3I; (iii) (a) *s*-BuLi/TMEDA, −78 °C, THF, 1 h, (b) **4a**; (iv) $(COOH)_2$, THF/H_2O (4/1 v/v).

SCHEME 4[a]



[a] Key: (i) (a) $C_2H_5C(OEt)_3$, $(CH_2)_2Cl_2$, 70 °C, (b) LDA, −78 °C, THF, (c) CH_3I; (ii) (a) *s*-BuLi/TMEDA, −78 °C, THF, (b) **4a**,**b**.

(7) The presence of the spirocyclic compounds **5d**,**e**, which equilibrate to the corresponding hydroxylamino forms in solution, was ascertained by NMR spectroscopy. ^{13}C NMR, indeed, showed two diagnostic signals: the spiro carbon at around 120 ppm and the C=N carbon at around 165 ppm; two species were revealed by ^{1}H NMR spectra as well (see the Supporting Information).

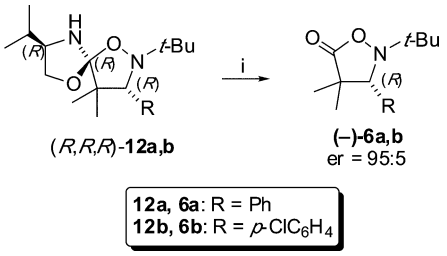
(8) In the course of the reduction of **6b** the chlorine atom was lost and **7a** was the only isolated product. There are other cases concerning the loss of a halogen atom under reduction conditions, see: McQuillin, F. J.; Ord, W. O. *J. Am. Chem. Soc.* **1959**, *81*, 9−3172.

(9) Kamata, K.; Agata, I., Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 3113−3116.

(10) Hydroxylamine (*R*,*R*)-**10** was isolated and characterized after column chromatography by FT-IR analysis (bands at 3373 cm^{-1}, OH, and 1690 cm^{-1}, C=N) and ^{13}C NMR (see the Supporting Information). Compound (*R*,*R*)-**10** was found to equilibrate in $CDCl_3$ or acidic solution to the corresponding spirocyclic form whose hydrolysis gave the 5-isoxazolidinone (−)-**6a** (er determinated by chiral GC, see the Supporting Information).

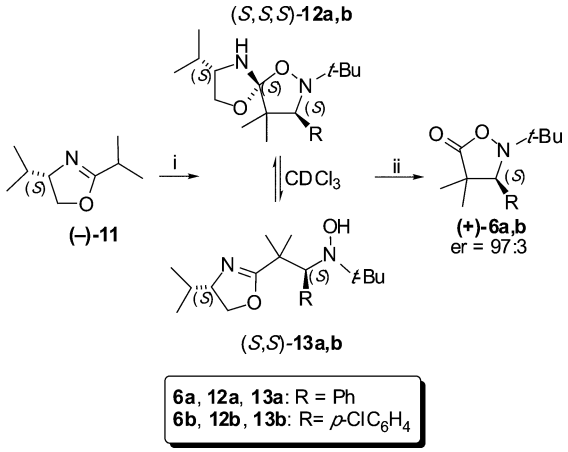
(11) The X-ray analysis of (*R*,*R*,*R*)-**12a** allowed the determination of the absolute configuration at the newly created stereogenic centers. CCDC-213766 contain the supplementary crystallographic data for compound (*R*,*R*,*R*)-**12a**. These data can be obtained free of charge at www.ccdc.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (int) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk.

SCHEME 5[a]



[a] Key: (i) CF_3COOH, 1,4-dioxane/H_2O (4/1 v/v).

SCHEME 6[a]



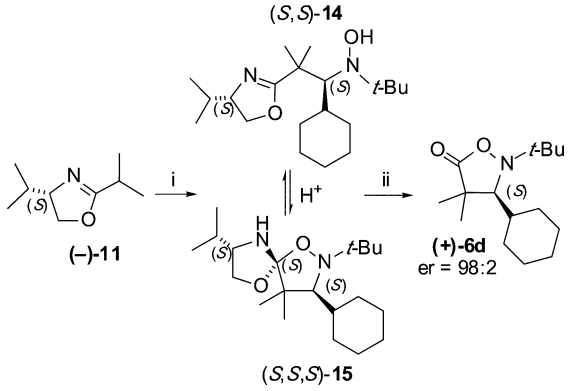
[a] Key: (i) (a) *s*-BuLi/TMEDA, −78 °C, THF, (b) **4a,b**; (ii) CF_3COOH, 1,4-dioxane/H_2O (4/1 v/v).

6b (er 95/5) was obtained (>98% yield) by hydrolysis of the spirocyclic compound (*R*,*R*,*R*)-**12b** (R = *p*-ClC_6H_4) which in turn was prepared from oxazoline (+)-**11** and nitrone **4b** (Scheme 5).[13]

To our gratification and as expected, 5-isoxazolidinones of opposite configuration with respect to (−)-**6a**,**b** were obtained starting from (4*S*)-2,4-diisopropyl-2-oxazoline (−)-**11**, which was prepared from L-valinol following the procedure adopted for the synthesis of oxazolines **2**, (+)-**9**, and (+)-**11**. Indeed, compound (−)-**11**, once lithiated, reacted with nitrones **4a**,**b** to give spirocyclic compounds (*S*,*S*,*S*)-**12a**,**b** and then, after hydrolysis, 5-isoxazolidinones (+)-**6a**,**b** [(+)-**6a**, 78% yield; (+)-**6b**, >98% yield] all highly enantiomerically enriched (er 97/3) (Scheme 6).

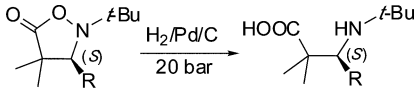
The reaction of lithiated oxazoline (−)-**11** with cyclohexylnitrone **4d** afforded the hydroxylamino derivative (*S*,*S*)-**14** (40% yield) after flash chromatography highly diastereoselectively. The structure of (*S*,*S*)-**14** was proved by IR and ^{13}C NMR analysis.[14] Its hydrolysis with oxalic acid furnished the 5-isoxazolidinone (+)-**6d** highly enantioenriched (er 98/2) (Scheme 7) through the corresponding spirocyclic form (*S*,*S*,*S*)-**15**.[15] It seems, therefore, as

SCHEME 7[a]



[a] Key: (a) *s*-BuLi/TMEDA, −78 °C, THF, (b) **4d**; (ii) $(COOH)_2$, THF/H_2O (4/1 v/v).

TABLE 2. Preparation of β-Amino Acids 7



5-isoxazolidinone (+)-**6**	R	β-amino acid **7** (% yield)[a]
(+)-**6a**	Ph	(+)-**7a** (>98)
(+)-**6b**	*p*-ClC_6H_4	(−)-**7a**·HCl (>98)[b]
(+)-**6d**	Cy	(−)-**7c** (>98)

[a] Isolated yields after column chromatography. [b] The chlorine atom was lost in the reduction of (+)-**6b,** and the amino acid **7a** was obtained as a hydrochloride salt.

the spirocyclic compound which forms in the reaction of the lithiated oxazoline with nitrone equilibrates to the open hydroxylamino form depending upon the substituents which are present in the oxazoline ring and on the nitrone. What is useful, however, is that subsequent acidic treatment leads to the desired 5-isoxazolidinone.

Subsequently, we decide to convert the optically active 5-isoxazolidinones into the corresponding β-amino acids by the N−O reduction. The results are summarized in Table 2. It is worth pointing out that the reduction of 5-isoxazolidinone (+)-**6b** afforded the same β-amino acid **7a** (as a hydrochloride salt) obtained in the reduction of (+)-**6a** as a consequence of a loss of the *p*-chlorine atom in (+)-**6b** under the reaction conditions.[16] Other methods of preparation of chiral β-amino acids have been reported.[17] Our methodology, at least when aromatic nitrones are used, compares rather well.

In conclusion, this paper reports a new simple stereoselective and enantioselective synthesis of 5-isoxazolidinones which are precursors of β-amino acids, which are important targets in organic synthesis, by using the chemistry of lithiated 2-alkyl-2-oxazolines with nitrones.

(12) The er value of 5-isoxazolidinones (−)-**6a**,**b** were determined by chiral GC on a β-cyclodextrin capillary column. The retention time of (−)-**6a** was the same observed in the case of the 5-isoxazolidinone derived from the hydrolysis of (*R*,*R*)-**10**, thus confirming its absolute configuration (*R*) at C-3.

(13) 5-Isoxazolidinone (−)-**6b** was tentatively assigned the *R* configuration by comparison of its GC retention time (first eluted) and the sign of its optical rotation with those of the known (−)-**6a** (see the Supporting Information).

(14) The presence of two bands at 3272 (OH stretching) and at 1697 cm^{-1} (C=N stretching) in the FT-IR spectrum and a carbon at 168 ppm in the ^{13}C NMR spectrum are diagnostic of the presence of the hydroxylamino form (*S*,*S*)-**14**.

(15) The absolute configuration of (+)-**6d** was assigned by analogy with those of (+)-**6a**,**b**.

(16) As a prove of the formation of (−)-**7a**·HCl in the reduction of (+)-**6b**, a hydrochloride salt was generated from the β-amino acid (+)-**7a** derived from (+)-**6a**. These two salts showed similar ^1H, ^{13}C NMR, FT-IR, and $[\alpha]_D$ (see the Supporting Information).

Highly enantiomerically enriched 5-isoxazolidinones and *β*-amino acids of opposite configuration can be prepared simply by changing the chirality of the starting 2-isopropyl-2-oxazoline. Limitations of the above methodology reside in the nitrone *tert*-butyl *N*-protection and the low yields of the reactions that use alkyl nitrones. More interesting results are expected from the coupling reaction of lithiated 2-alkyl-2-oxazolines carrying an α-stereocenter that should lead to α,α′-disubstituted *β*-amino acids. Work is in progress to this end, and results will be reported in due course.

Acknowledgment. This work was carried out under the framework of the National Project "Stereoselezione in Sintesi Organica, Metodologie ed Applicazioni" and the FIRB Project "Progettazione, preparazione e valutazione biologica e farmacologica di nuove molecole organiche quali potenziali farmaci innovativi" supported by the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, Rome) and by the University of Bari and CNR (Rome). We are also grateful to Prof. Marcel Pierrot of the Centre Scientifique Saint-Jerome, Marseille, France, for performing X-ray analysis on compound (*R*,*R*,*R*)-**12a**.

Supporting Information Available: General procedures for the preparation of 2-isopropyl-2-oxazolines **2**, (+)-**9** and (+)/(−)-**11** (S2), of spirocyclic compounds **5** (S2), of 5-isoxazolidinones **6** (S9), and of *β*-amino acids **7** (S12). Spectroscopic and physical data for compounds **5a**−**e** (S3−S5), **6a**−**e** (S9−S12), **7a**−**d** (S12,S13), **10** (S6), **12a**,**b** (S7,S8), **13a**,**b** (S7,S8), and **14** (S9) and an ORTEP view of the spirocyclic compound (*R*,*R*,*R*)-**12a** (Figure S1, S12). This material is available free of charge via the Internet at http://pubs.acs.org.

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