Solid-Phase Synthesis of Isoxazole-Based Amino Acids: A New Scaffold for Molecular Diversity

Lidia De Luca, Giampaolo Giacomelli,* and Antonella Riu

Dipartimento di Chimica, Università degli Studi di Sassari, via Vienna 2, I-07100 Sassari, Italy

ggp@ssmain.uniss.it

Received May 15, 2001

The rational design of therapeutic agents that overcome the pharmacological limitations of peptides is one of the major goals of medicinal chemistry. For this reason, peptidomimetics have become very important for organic and medicinal chemistry. Potentially useful peptidomimetics should resist in vivo hydrolysis and present some conformational bias.[1] With this goal in mind, several building blocks able to stabilize some parts of the peptide chain have been developed.[2]

In recent years, we have reported the preparation of heterocycle-containing optically active amino acids as chiral building blocks for the design of peptidomimetics.[3] Searching for new molecules that might be assembled with themselves and/or other substrates using combinatorial techniques, we propose here a new scaffold containing an isoxazole moiety (Figure 1), following the strategy of creating a rigid core molecule carrying different functional groups that could be subsequently functionalized with different building blocks to generate a library of molecular diversomers.

For the preparation of this compound, we envisioned that the use of solid-phase 1,3-dipolar cycloaddition would be a good alternative to the classical synthesis. The synthesis of isoxazoles on trityl chloride resins has been described earlier using polymer-supported nitrile oxide precursors.[4] However, we have decided to test the possibility of preparing isoxazoles and in particular compounds such as **A** by anchoring the acetylenic compounds[5] on the resin and generating the nitrile oxide in situ from suitable carbonyl compounds. Our efforts at obtaining a representative library of isoxazoles are presented below.

Alkynyl alcohol **1** was anchored on trityl chloride resin (Scheme 1). The loading was controlled by monitoring via infrared spectroscopy for the appearance of the alkyne stretch at 3300 cm^{-1} and determined (∼45% after 12 h) by recovering the alkyne after cleavage of a small portion of the resin. The loading was complete after 48 h at room temperature. After being washed, the resin **2** was treated with 8 equiv of the aldoxime **3** and of *N*-chlorosuccinimide (NCS) in methylene chloride in a one-pot three-component reaction.

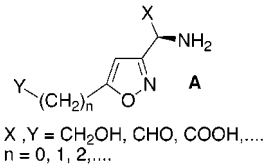


Figure 1.

Successively, triethylamine was added slowly and dropwise over a period of 2 h to generate the nitrile oxide. The resulting mixture was shaken at room temperature and monitored by infrared spectroscopy for the disappearance of the alkyne stretch (ca. 24 h). The resin was then filtered, washed, and dried. The isoxazole **5** was cleaved off the resin **4** under standard conditions (5% TFA in CH_2Cl_2).

A library of isoxazoles (Figure 2) was thus generated by trapping in situ the anchored alkyne with the nitrile oxide generated by the appropriate aldehyde, in a practical one-pot operation. The yields were satisfactory (60%−90%), and the purity of recovered compounds after cleavage were greater than 95%. In every case, only one isomer was recovered.

The potential of the procedure was emphasized by the synthesis of compounds **5i**−**k**, derived from amino aldehydes obtained from the corresponding amino acids. In particular, compounds **5j** and **5k** are very versatile intermediates and can potentially be used for developing an isoxazole-based library of new amino acids.

This has been demonstrated by carrying out several transformations of the compound **5j**, generating a series of diversomers (Scheme 2).

Thus, polymer-supported isoxazole derivative **4j** was successfully converted to other functionalized derivatives; cleavage of the oxazoline ring by *p*-toluenesulfonic acid (PTSA)[3d] in dry methanol, followed by oxidation using Jones' conditions,[6] afforded resin-bound amino acid **6**,[7] which gave amino acid derivative **10** in a 56% yield upon treatment with TFA 5%. In addition, compound **5j** was oxidized to the carbaldehyde **8** and to the carboxylic acid **9**, respectively, under Swern (90%)[8] and Jones' (95%) conditions. The oxidative process carried out on compound **7** furnished the bicarboxyl amino acid **11** (41%). Similar reactions might be obviously carried out on compound **4k**. It is noteworthy that compounds **7**, **9**, and **10** represent valuable examples of a rigid core molecule for generating molecular diversomers.

In summary, 1,3-dipolar cycloaddition methodology for the preparation of structurally different isoxazoles and

(1) See, for example: Gante, I. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. Liskamp, R. M. J. *Recl. Trav. Chim. Pays*−*Bas* **1994**, *113*, 1.

(2) Apella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, J. J.; Gellman, S. H. *Nature* **1997**, *387*, 381 and references therein.

(3) (a) De Luca, L.; Giacomelli, G.; Porcheddu, A.; Spanedda, A. M.; Falorni, M. *Synthesis* **2000**, 1295. (b) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Dettori, G. *Eur. J. Org. Chem.* **2000**, 3217. (c) De Luca, L.; Falorni, M.; Giacomelli, G.; Porcheddu, A. *Tetrahedron Lett.* **1999**, *40*, 8701. (d) Falorni, M.; Giacomelli, G.; Spanu, E. *Tetrahedron Lett.* **1998**, *39*, 9241. (e) Falorni, M.; Giacomelli, G.; Spanedda, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3039.

(4) (a) Shankar, B. B.; Yang, D. Y.; Girton, S.; Ganguly, A. K. *Tetrahedron Lett.* **1998**, *39*, 2447. (b) Batra, S.; Rastogi, S. K.; Kundu, B.; Patra, A.; Bhaduri, A. P. *Tetrahedron Lett.* **2000**, *41*, 5971.

(5) Kantorowski, E. J.; Kurth, M. J. *J. Org. Chem.* **1997**, *62*, 6797.

(6) Reginato, G.; Mordini, A.; Caracciolo, M. *J. Org. Chem.* **1997**, *62*, 6187.

(7) Although the trityl chloride resin was known to be acid-labile, under the experimental conditions adopted, no detectable cleavage of the resin was detected. Moreover, as reported in the literature, the BOC group was also retained.[3c,d,5]

(8) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. Marx, M.; Tidwell, T. T. *J. Org. Chem.* **1984**, *49*, 788.

10.1021/jo015758v CCC: $20.00
Published on Web 08/31/2001

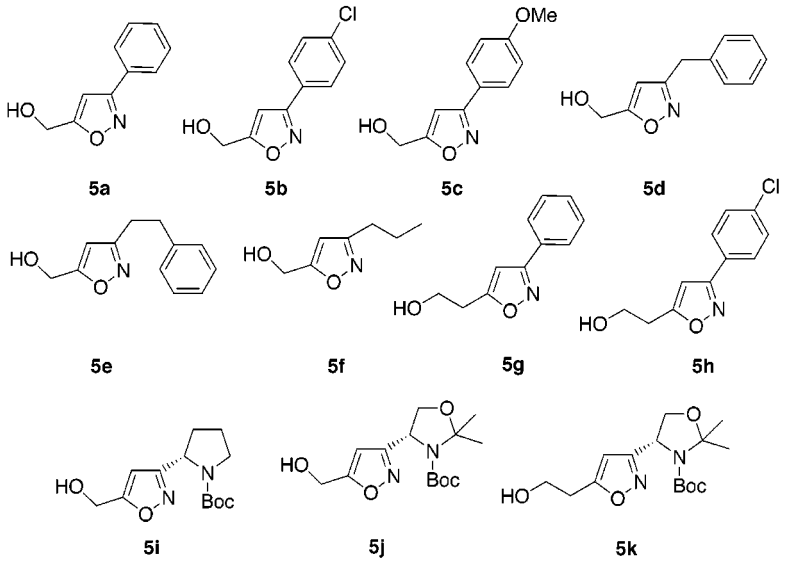
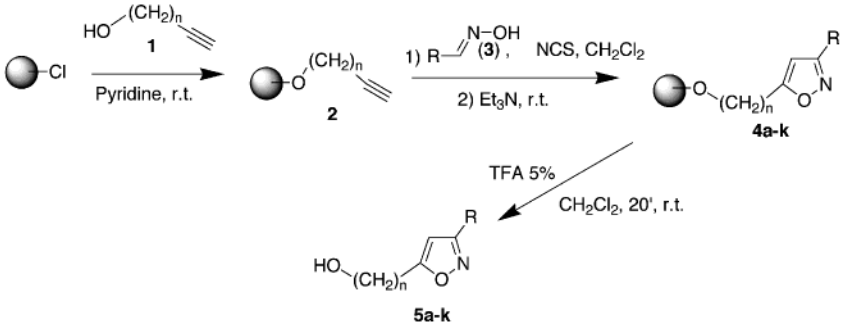
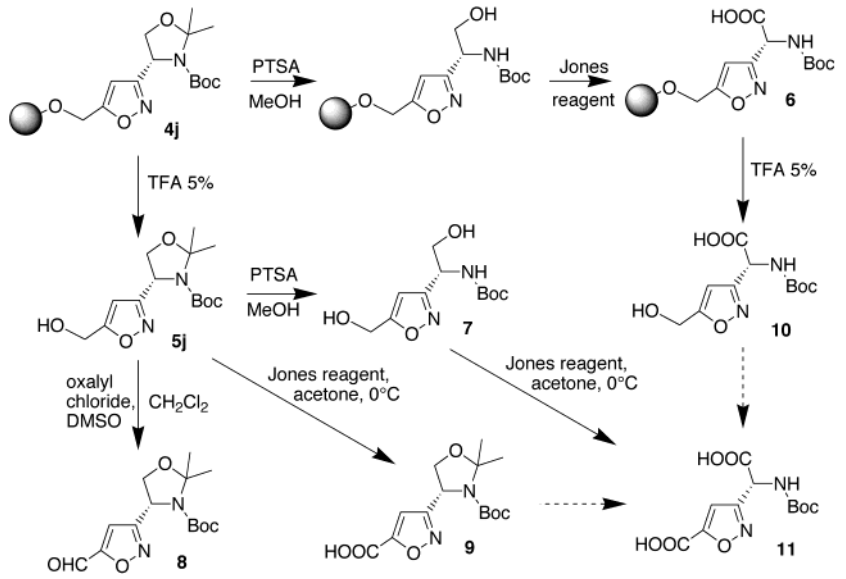


Figure 2.

Scheme 1



Scheme 2



a series of isoxazole-based amino acids was developed under solid-phase conditions. It is worth pointing out that compounds **8** and **9** are excellent substrates, which can be further diversified to obtain an array of isoxazole-based novel compounds. Moreover, successive transformation on **9**, **10**, and respective homologues ($n > 1$) should lead to the formation of amino acids similar to **11**, which can be regarded as glutamic acid homologues.

Experimental Section

All of the solvents and the reagents were used in the commercially available grade of purity. The N-protected amino acids were prepared according standard methods, and their purity was established before utilization by melting point and optical rotation. The aldehydes were commercial products or were prepared from amino acids through known procedures.[9] Oximes were prepared by reaction of the aldehydes with

hydroxylamine in the presence of pyridine in MeOH at room temperature. The ^{1}H NMR and ^{13}C NMR were obtained at 300 and 75.4 MHz from $CDCl_3$ solutions.

General Procedure for the Solid-Phase Preparation of Isoxazoles. The syntheses were carried out in a manual 20 mL reactor equipped with a sintered glass and using a nitrogen flow for agitation and filtration. A solution of alkynyl alcohol **1** (7.4 mmol) in dry pyridine (3.0 mL) was added dropwise to trityl chloride resin (0.35 g of a 1.24 mmol/g Novabiochem sample, 0.43 mmol, swollen in CH_2Cl_2) in 7.0 mL of pyridine. The mixture was shaken at room temperature for 48 h, filtered, washed several times with pyridine and dry diethyl ether, and dried to afford the corresponding alkyne resin **2**. FTIR (KBr): 3289 cm^{-1}. The resin was then separated into portions for the construction of the library.

To the resin (0.16 mmol), swollen with CH_2Cl_2, were added CH_2Cl_2 (5.0 mL), oxime **3** (1.72 mmol), and *N*-chlorosuccinimide (0.9 g, 6.9 mmol); after 2 h, Et_3N (1 mL, 7.2 mmol) was added dropwise, and the mixture was shaken at room temperature and monitored for the disappearance of the alkyne stretch (24 h). The resin was then filtered and washed several times with CH_2Cl_2 affording polymeric isoxazoles **4a**−**k**. Substrate cleavage was accomplished by treating **4** with a freshly prepared TFA/CH_2Cl_2 (5:95) solution at room temperature (20 min). Filtration and resin washing with CH_2Cl_2 gave an organic phase, which was washed with Na_2CO_3 aqueous 10% solution and dried (Na_2SO_4). Removal of the solvent gave the target isoxazoles **5a**−**k** in 60%−90% yield.

Preparation of the Polymeric Amino Acid 6 and of Compound 10. A sample of resin **4j** prepared from trityl chloride resin (0.35 g), propargyl alcohol (0.41 g, 7.4 mmol), and the oxime of Garner's aldehyde (0.42 g, 1.72 mmol) in THF (10 mL) was treated with *p*-toluenesulfonic acid (0.04 g, 0.2 mmol). The mixture was shaken at room temperature for 36 h untila test for detection of OH group was positive.[10] The resin was then filtered and washed several times with THF and CH_2Cl_2 and then rinsed with THF/acetone 1:1. The mixture was cooled at 0 °C and treated with 0.2 mL of Jones' reagent and shaken at room temperature. A few beads of the resin were tested for the presence of free COOH groups;[11] after 12h, the test being positive, the resin **6** was filtered and washed with THF followed by CH_2Cl_2. Then, the resin was cleaved as above; filtration gave an organic phase, which was treated with Na_2CO_3 aqueous 10% solution. The aqueous phase was collected, washed with diethyl ether and with HCl 1 N, extracted with CH_2Cl_2, and dried (Na_2SO_4). Removal of the solvent gave 0.066 g of *N*-*tert*-butoxycarbonylamino-(5-methanolisoxazol-3-yl)acetic acid **10**. ^{1}H NMR: δ 11.4 (s, 1H), 7.92 (s, 1H), 6.27 (s, 1H), 5.75 (s, 1H), 5.07 (bs, 1H), 4.71 (s, 2H), 1.44 (s, 9H). ^{13}C NMR: δ 176.5, 162.8, 158.9, 150.0, 99.5, 71.2, 65.2, 62.7, 28.7. Anal. Calcd for $C_{11}H_{16}N_2O_6$ (272.25): C, 48.53; H, 5.92; N, 10.29. Found: C, 48.71; H, 5.92; N, 10.22.

Acknowledgment. The work was financially supported by the University of Sassari (Fondi 60%).

Supporting Information Available: ^{1}H and ^{13}C spectra of compounds **5a**−**k** and the preparation of compounds **7**−**9** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO015758V

(9) Garner, P.; Park, J. M. *J. Org. Chem.* **1991**, *56*, 18.

(10) Attardi, M. E.; Falchi, A.; Taddei, M. *Tetrahedron Lett.* **2000**, *41*, 7395. Attardi, M. E.; Taddei, M. *Tetrahedron Lett.* **2001**, *42*, 2927.

(11) Attardi, M. E.; Porcu, G.; Taddei, M. *Tetrahedron Lett.* **2000**, *41*, 7391.