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Ammonium Chloride Promoted Three-Component Synthesis of 5-Iminooxazoline and Its Subsequent Transformation to Macrocyclodepsipeptide

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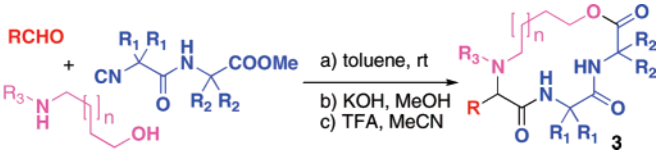
ABSTRACT



A three-component reaction of an α,α-disubstituted α-isocyanoacetamide, an aldehyde and an amino alcohol afforded the 5-iminooxazoline, which, upon saponification, cyclized under acidic conditions to provide the macrocyclodepsipeptide in good overall yield.

Over the past decades, a multitude of efficient synthesis strategies have been developed enabling the rapid construction of complex structures under mild conditions.[1] At the forefront of these chemical methodologies are multicomponent reactions (MCRs),[2] which create molecular complexity and diversity from readily accessible starting materials in one single operation. The isocyanide capable of reacting with both nucleophile and electrophile is an ideal starting material for the development of novel MCRs[2] and indeed formed the basis of the well-known Passerini[3] and Ugi reactions.[4] A conceptually simple approach to further increase the versatility of these powerful transformations is the use of functionalized isocyanides. We have been exploiting the peculiar reactivity profiles of α-isocyanoacetamides,[5] α-isocyanoacetic acids,[6] *O*-isocyanobenzamides,[7] and α-isocyanoacetates[8,9] and have developed a number of MCRs allowing rapid access to the medicinally relevant heterocycles.[10] As a logical extension of our work in this field, we report herein a three-

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(1) For reviews see: (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (c) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.* **1997**, 765−769. (d) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969. (e) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134−7186.

(2) (a) For a monograph see: *Multicomponent Reaction*: Zhu, J.; Bienaymè, H. Eds.; Wiley-VCH: Weinhein, Germany, 2005. For recent reviews: (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51-80. (c) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133−1144. (d) Orru, V. A.; De Greef, M. *Synthesis* **2003**, 1471−1499. (e) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957−4980. (f) Dömling, A. *Chem. Rev.* **2006**, *106*, 17-89. (g) D'Souza, M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095−1108. (h) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602−1634. (i) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570−1581.

(3) (a) Banfi, L.; Riva, R. *Organic Reactions;* Charette, A. B., Ed.; John Wiley & Sons Inc.: New York, 2005; *65*, pp 1−140. (b) Oxidative P-3CR, see: Ngouansavanh, T.; Zhu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3495−3497.

(4) (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168-3210. (b) Wessjohann, L. A.; Voigt, B.; Rivera, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4785−4790. (c) El Kaim, L.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *45*, 7961−7964. (d) Giovenzana, G. B.; Tron, G. C.; Di Paola, S.; Menegotto, I. G.; Pirali, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1099−1102. (e) Ngouansavanh, T.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5775−5778.

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component reaction of α,α-disubstituted α-isocyanoacetamides (**1**)[11] with an aldehyde and an amine leading to 5-iminooxazoline (**2**) (Figure 1). The structural features incorporated in **1**, that is, a secondary amide and a double substitution at the α-position, were designed to guarantee the occurrence of the projected reaction sequence. We document also the subsequent transformation of **2** to macrocyclodepsipeptide (**3**) under mild acidic conditions by using the 5-iminooxazoline as an internal activator of the vicinal carboxylic acid.

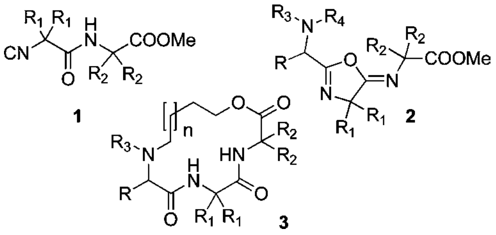
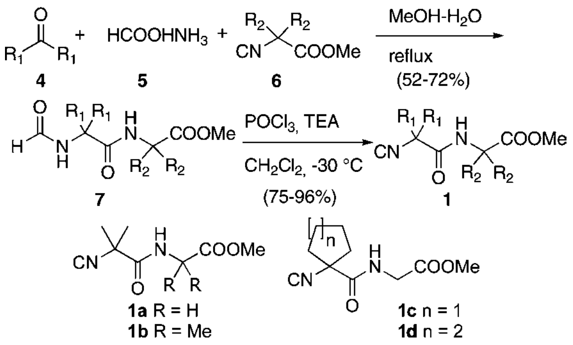


Figure 1. From α,α-disubstituted α-isocyanoacetamide to 5-iminooxazoline and macrocyclodepsipeptide.

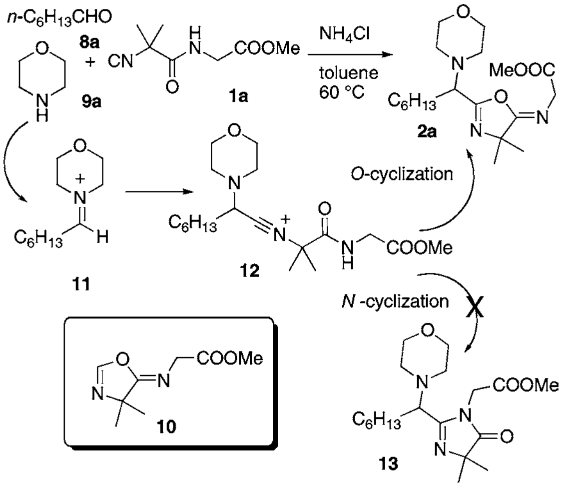
The requisite α,α-disubstituted α-isocyanoacetamides (**1**) are prepared as shown in Scheme 1. The Ugi reaction of ketone (**4**), ammonium formate (**5**), and isocyanoacetate (**6**) in methanol at 60 °C[11] afforded the adduct **7**. Dehydration of formamide **7** (POCl$_3$, TEA, CH$_2$Cl$_2$, −30 °C)[12] yielded the desired isocyanide (**1**) in excellent yield (Scheme 1). Four dipeptidic α,α-dialkyl α-isocyanoacetamides were synthesized following this two-step sequence with overall yields ranging from 45% to 60%. It is interesting to note that the Ugi reaction does not suffer from steric effects[13] and that this protocol could potentially constitute a very efficient way for the synthesis poly-Aib (α-aminoisobutyric acid) peptides, not easily accessible by conventional peptide chemistry.[14]

Scheme 1. Synthesized α,α-Disubstitued α-Isocyanoacetamides



The reaction of **1a** with heptanal (**8a**) and morpholine (**9a**) was next examined. In methanol, the undesired isomerization of **1a** took place predominantly to afford the 5-iminooxazoline **10** in 47% yield. Gratifyingly, when the reaction was performed in toluene in the presence of ammonium chloride,[5,15] a three-component condensation occurred to provide the 5-iminooxazoline (**2a**) in 62% isolated yield.[16] A plausible reaction scenario that accounts for the formation of **2a** is shown in Scheme 2. Thus, condensation of **8a** and **9a** would give the iminium ion **11**, which would react with isonitrile (**1a**) to afford the nitrilium intermediate (**12**).

Scheme 2. Three-Componenent Synthesis of 5-Iminooxazoline



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(5) (a) Sun, X.; Janvier, P.; Zhao, G.; Bienaymè, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877−880. (b) Janvier, P.; Sun, X.; Binaymè, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560−2567. (c) Fayol, A.; Housseman, C.; Sun, X.; Janvier, P.; Bienaymè, H.; Zhu, J. *Synthesis* **2005**, 161−165. (d) Tron, G. C.; Zhu, J. *Synlett* **2005**, 532−534. (e) Janvier, P.; Bois-Choussy, M.; Bienaymè, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 811−814. (f) Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2006**, *8*, 4145−4148.

(6) (a) Bonne, D.; Dkhane, M.; Zhu, J. *Org. Lett.* **2004**, *6*, 4771−4774. (b) Bonne, D.; Dekhane, M.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560−2567.

(7) Bonne, D.; Dekhane, M.; Zhu, J. *Org. Lett.* **2005**, *7*, 5285−5288.

(8) Bonne, D.; Dekhane, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2485−2488.

(9) (a) Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; De Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Org. Lett.* **2003**, *5*, 3759−3762. (d) Marcaccini, S.; Torroba, T. *Org. Prep. Proc. Int.* **1993**, *25*, 141−208.

(10) (a) Gámez-Montaño, R.; Zhu, J. *J. Chem. Soc., Chem. Commun.* **2002**, 2448−2449. (b) Fayol, A.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3633−3635. (c) Janvier, P.; Bienaymé, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4291−4294. (d) Gámez-Montaño, R.; González-Zamora, E.; Potier, P.; Zhu, J. *Tetrahedron* **2002**, *58*, 6351−6358. (e) Fayol, A.; Zhu, J. *Org. Lett.* **2005**, *7*, 239−242.

(11) (a) Bossio, R.; Marcaccini, S.; Paoli, P.; Papaleo, S.; Pepino, R.; Polo, C. *Liebigs Ann. Chem.* **1991**, 843−849. (b) Costa, S. P. G.; Maia, H. L. S.; Peerira-Lima, S. M. M. A. *Org. Biomol. Chem.* **2003**, *1*, 1475−1479.

(12) (a) Obrecht, R.; Hermann, R.; Ugi, I. *Synthesis* **1985**, 400−402. (b) Zhao, G.; Bughin, C.; Bienaymé, H.; Zhu, J. *Synlett* **2003**, 1153−1154.

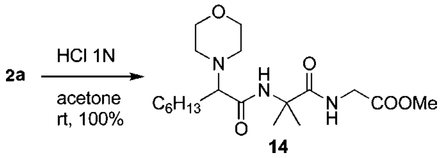
(13) For an interesting exemple see: Yamada, T. *Synthesis* **1998**, 991−998.

(14) Toniolo, C.; Formaggio, F.; Kaptein, B.; Broxterman, Q. B. *Synlett* **2006**, 1295−1310.

(15) (a) Cristau, P.; Vors, J. P.; Zhu, J. *Org. Lett.* **2001**, *3*, 4079−4082. (b) Cristau, P.; Vors, J. P.; Zhu, J. *Tetrahedron* **2003**, *59*, 7859−7870. (c) Parchinsky, V. Z.; Shuvalova, O.; Ushakova, O.; Kravchenko, D. V.; Krasavin, M. *Tetrahedron Lett.* **2006**, *47*, 947−951. (d) Neo, A. G.; Carrillo, R. M.; Barriga, S.; Momán, E.; Marcaccini, S.; Marcos, C. F. *Synlett* **2007**, 327−329. (e) Umkehrer, M.; Ross, G.; Jäger, N.; Burdack, C.; Kolb, J.; Hu, H.; Alvim-Gaston, M.; Hulme, C. *Tetrahedron Lett.* **2007**, *48*, 2213−2216.

Trapping of the latter by the internal amide oxygen would produce the 5-iminooxazoline (**2a**). The alternative nucleophilic attack by nitrogen leading to imidazolinone **13** was not observed, probably due to the hard electropilic nature of the nitrilium intermediate.[7,17] The structure of **2a** was confirmed by its hydrolysis under mild acidic conditions (1 N HCl, acetone, room temperature) affording the tripeptide **14** in a quantitative yield (Scheme 3).[18] Only one isomeric form of **2a** was detected in its ^{1}H NMR spectrum and the *Z*-geometry was tentatively assigned for the imidate unit based on the steric consideration. We stress the importance of α,α-disubstitution pattern in **1** since the reaction of secondary amide derived from α-mono substituted α-isocyanoacetamide with aldehyde and amine led only to a complex reaction mixture.

Scheme 3. Acidic Hydrolysis of 5-Iminooxazoline



The scope of this protocol was next examined by varying the structure of aldehydes, amines, and isocyanides. The reaction turned out to be quite general and a variety of functionalities such as acetate, free hydroxy group, carbamate, and esters are tolerated. The spiro iminooxazoline was readily accessible starting from isocyanides **1c** and **1d** (Figure 2). The reaction appeared to be clean and proceeded with complete conversion of the substrates as demonstrated by NMR analysis of the crude reaction mixture. The moderate isolated yields were due to their partial degradation during purification. Indeed, 5-iminooxazolines are known to be very sensitive to the acid, and flash chromatography has to be performed using neutral alumina (Brockmann grade III) as support. Nine other iminooxazolines were synthesized and were engaged, without purification, in the subsequent transformations (cf. Figure 3).

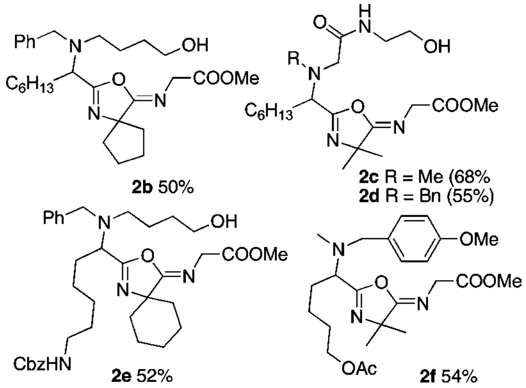


Figure 2. Three-component synthesis of 5-iminooxazoline.

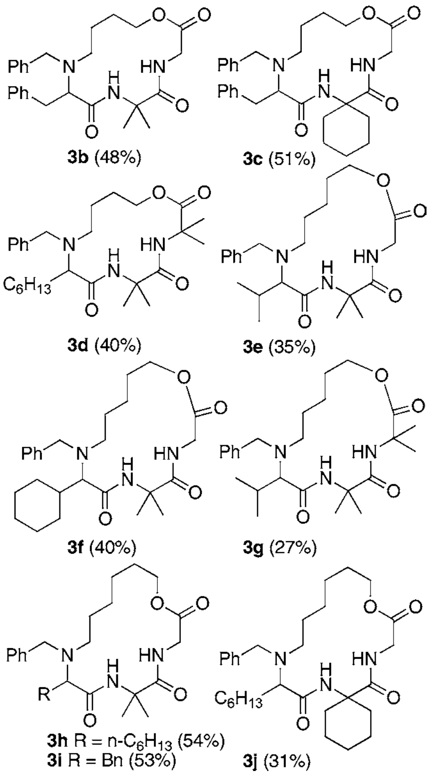


Figure 3. Synthesized macrocyclodepsipeptides.

A hydrochloride salt of amine can be used as a starting material in the presence of triethylamine. We assumed that the stoichiometric amount of Et$_3$N·HCl generated in situ played the same role as ammonium chloride in promoting the three-component reaction.

Besides its hydrolysis to peptide, little is known about the chemistry of 5-iminooxazoline. In analogy to the 5-amino oxazole, we speculated that we might be able to use this heterocycle as an internal activator of the vicinal carboxylic acid and consequently, develop an efficient macrocyclization protocol (Scheme 4).[19] The projected reaction sequence is

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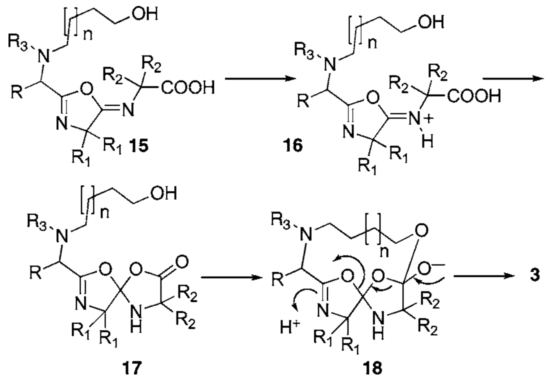
(16) Only fewer syntheses of iminooxazoline are known, see : (a) Middleton, W. J.; Krespan, C. G. *J. Org. Chem.* **1968**, 3625−3627. (b) Jackson, B.; Gakis, N.; Märky, M.; Hanse, H.-J.; von Philipsborn, W.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 916−918. (c) Grutzmacher, H.; Roesky, H. W. *Chem. Ber.* **1986**, *119*, 2127−2134. (d) Koksch, B.; Mutze, K.; Osipov, S. N.; Golubev, A. S.; Burger, K. *Tetrahedron Lett.* **2000**, *41*, 3825−3838.

(17) The attack of the amide nitrogen to isocyanide to yield imidazolinone has been reported under strong basic conditions see: (a) Matsumoto, K.; Suzuki, M.; Yoneda, N.; Miyoshi, M. *Synthesis* **1977**, 249−250. (b) Bossio, R.; Marcaccini, S.; Papaleo, S.; Pepino, R. *J. Heterocycl. Chem.* **1994**, *31*, 397−399.

(18) Imidazolinones are stable under acidic conditions, see: Rouchaud, J.; Gustin, F.; Moulard, C. *Bull. Soc. Chim. Belg.* **1992**, *101*, 959−968.

(19) (a) Zhao, G.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2001**, *123*, 6700−6701. (b) Bughin, C.; Zhao, G.; Bienaymè, H.; Zhu, J. *Chem. Eur. J.* **2006**, *12*, 1174−1184. (c) Bughin, C.; Masson, G.; Zhu, J. *J. Org. Chem.* **2007**, *72*, 1826−1829.

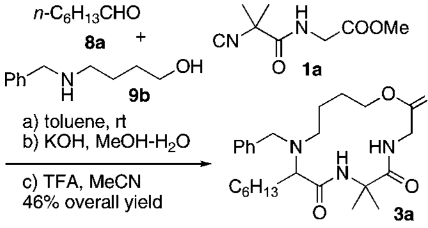
Scheme 4. Macrocyclization Using 5-Iminooxazoline as an Internal Activator of the Terminal Carboxylic Acid



depicted in Scheme 4. Thus protonation of exocyclic imine would provide the iminium species **16** that could be trapped either by an external nucleophile (H_2O) leading to simple hydrolysis or under favorable circumstance, by the neighboring carbonyl oxygen leading to spirolactone (**17**). Being highly electrophilic, the carbonyl carbon of intermediate **17** could subsequently be attacked by the tethered nucleophile leading to, after fragmentation, the desired macrocyclodepsipeptide (**3**).[20] The formation of spirolactone could in principle reduce the entropy loss during the cyclization and consequently favor the macrocyclization.[21]

The realization of this transformation is shown in Scheme 5. The three-component reaction of **1a**, **8a**, and amino alcohol **9b** afforded the expected 5-iminooxazoline which, without purification, was hydrolyzed (1.0 equiv KOH, MeOH−H_2O, room temperature) to the corresponding carboxylic acid. To our delight, stirring an acetonitrile solution of the crude carboxylic acid ($c = 0.001$ M) in the presence of trifluoroactetic acid (50 equiv) afforded the macrocyclodepsipeptide **3a** in 46% overall yield.

Scheme 5. Macrolactonization under Acidic Conditions



The macrocycles synthesized by this three-step sequence are listed in Figure 3. As is seen, the 14-, 15-, and 16-membered macrocycles (**3b**−**j**) with different substituents at the peripheral of the cycle were readily synthesized starting from simple aldehydes, amines, and dipeptidic isocyanides in overall yields ranging from 27 to 54%. Even with sterically very hindered substrates, cyclization still worked to provide the desired macrocycles (**3d**,**g**). Although the overall yield was moderate, the chemical yield per chemical bond produced remained excellent (1 C−C, 1 C−N, 1 C−O in 3CR and 1 C−O in macrocyclization).

In summary, we have developed a new three-component synthesis of 5-iminooxazolines starting from aldehydes, amines, and α,α-disubstituted α-isocyanoacetamides and documented their subsequent transformation to macrocycles. The entire sequence was realized under very mild conditions without using exotic reagents. In the macrocyclization step, the 4,4-disubstituted 5-iminooxazoline, after serving as an internal activator of the vicinal carboxylic acid, was concurrently converted to α,α-disubstituted amino acid and became an integral part of the resulting peptide backbone. The chemistry developed herein could be particularly efficient for the synthesis of macrocyclopeptides having Aib residues that are otherwise not easily accessible.[22]

Acknowledgment. Financial support from CNRS, France, and M.I.U.R.−PRIN 2006, Italy, are gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) (a) Ballard, C. E.; Yu, H.; Wang, B. *Curr. Med. Chem.* **2002**, *9*, 471−498. (b) Sarabia, F.; Chammaa, S.; Ruiz, A. S.; Ortiz, L. M.; Herrera, F. J. L. *Curr. Med. Chem.* **2004**, *11*, 1309−1332. (c) Wessjohann, L. A.; Rüijter, E. *Top. Curr. Chem.* **2005**, *243*, 137−184.

(21) For a review on the conformation-directed macrocyclization, see: Blankenstein, J.; Zhu, J. *Eur. J. Org. Chem.* **2005**, 1949−1964.

(22) For an elegant synthesis of macrocyclodepsipeptide containing Aib residues see: (a) Heimgartner, H.; Arnhold, F. S.; Fritschi, S. P.; Koch, K. N.; Margirius, J. E. F.; Linden, A. *J. Heterocycl. Chem.* **1999**, *36*, 1539−1547. (b) Jeremic, T.; Linden, A.; Heimgartner, H. *Chem Biodiversity* **2004**, *1*, 1730−1761.