ORGANIC LETTERS

2007
Vol. 9, No. 17
3319−3322

An Unprecedented Pd-Catalyzed, Water-Promoted Sequential Oxidative Aminocarbonylation–Cyclocarbonylation Process Leading to 2-Oxazolidinones

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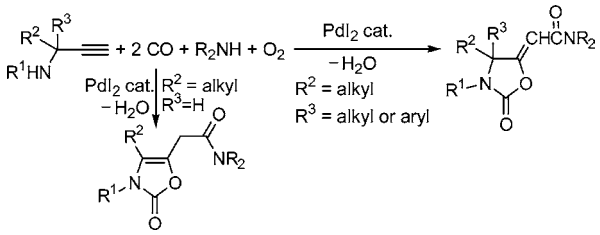
Received June 5, 2007

ABSTRACT



An unprecedented, PdI_2-catalyzed, sequential oxidative aminocarbonylation–cyclocarbonylation process, leading to 2-oxazolidinone derivatives 3 in good to excellent yields starting from readily available α,α-disubstituted 2-ynylamines 1 and secondary amines 2, is reported. In the case of an α-monosubstituted substrate, the initially formed 2-oxazolidinone derivative underwent shift of the double bond to give a 3*H*-oxazol-2-one derivative in excellent isolated yield.

2-Oxazolidinones are a very important class of heterocyclic compounds. Chiral 2-oxazolidinones are widely used as chiral auxiliaries in many important asymmetric syntheses;[1] moreover, oxazolidinone derivatives have shown important pharmacological properties, in particular as antibacterial agents.[2] The importance of these heterocyclic derivatives justifies the continuous efforts for developing novel approaches to their synthesis. A particularly attractive route to the formation of the 2-oxazolidinone core is based on annulation of a suitable acyclic precursor, which can allow the regioselective preparation of the final heterocycle with the desired substitution pattern.[3]

We report here a novel synthesis of 2-oxazolidinones **3** starting from readily available 2-ynylamines **1** and dialkyl-

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(1) For reviews, see: (a) Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron* **2005**, *61*, 8073−8094. (b) Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E.; Etxebarria, J. *Curr. Org. Chem.* **2005**, *9*, 219−235. (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 3−12. (d) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−875. (e) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23−32.

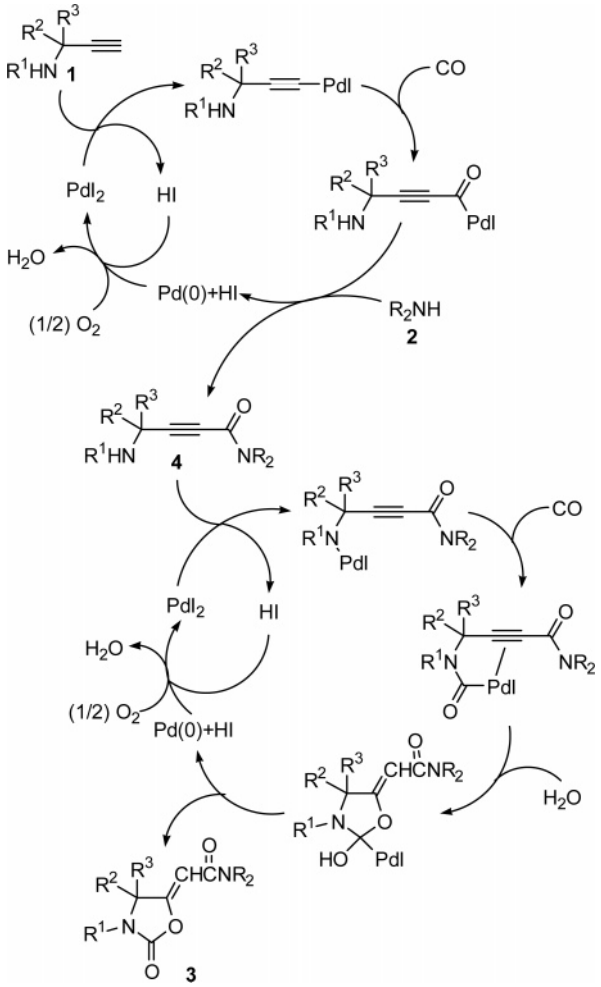
(2) For reviews, see: (a) Mukhtar, T. A.; Wright, G. D. *Chem. Rev.* **2005**, *105*, 529−542. (b) Hutchinson, D. K. *Expert Opin. Ther. Pat.* **2004**, *14*, 1309−1328. (b) Bozdogan, M.; Appelbaum, P. C. *Int. J. Antimicrob. Ag.* **2004**, *23*, 113−119. (c) Colizza, S.; Rossi, S.; Rodio, F.; Carnuccio, P.; Cucchiara G. *J. Chemother.* **2003**, 323−328. (d) Johnson, A. P. *Idrugs* **2003**, *6*, 240−245. (e) Barbachyn, M. R.; Ford, C. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010−2023. (f) Hutchinson, D. K. *Curr. Top. Med. Chem.* **2003**, *3*, 1021−1042. (g) Moellering, R. C. *Ann. Intern. Med.* **2003**, *138*, 135−142. (h) Diekema, D. J.; Jones, R. N. *Drugs* **2000**, *59*, 7−16. (i) Muller, M.; Schimz, K. L. *Cell. Mol. Life Sci.* **1999**, *56*, 280−285. (j) Brickner, S. J. *Curr. Pharm. Design* **1996**, *2*, 175−194.

(3) For a review on synthetic methods for the construction of the 2-oxazolidinone ring, see: Zappia, G.; Gacs-Baitz, E.; Delle Monache, G.; Misiti, D.; Nevola, L.; Botta, B. *Curr. Org. Synth.* **2007**, *4*, 81−135.

10.1021/ol071332c CCC: $37.00
Published on Web 07/26/2007

amines **2** through the concatenation of two catalytic cycles, both promoted by PdI_2, corresponding to oxidative aminocarbonylation of the triple bond followed by cyclocarbonylation (Scheme 1). To our knowledge, this is the first example of a sequential catalysis leading to 2-oxazolidinone derivatives starting from acyclic precursors.[4,5]

Scheme 1. Sequential Catalysis Leading to 2-Oxazolidinones **3**

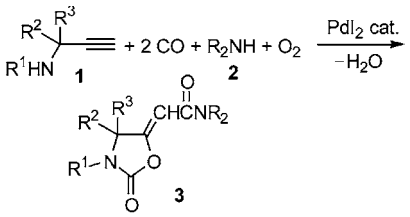


Our method consists of the reaction of α,α-disubstituted 2-ynylamines **1** with CO, O_2, and dialkylamines **2** in the presence of catalytic amounts of PdI_2 in conjunction with KI and H_2O (PdI_2/KI/**1**/**2**/H_2O molar ratio = 1:10:100:500: 500), in DME as the solvent at 100 °C and under 20 atm of a 4:1 mixture of CO/air.

As reported in Table 1, excellent yields of 5-(carbamoylmethylene)oxazolidin-2-ones **3** (84−98% by GLC, 80−95% isolated, entries 1−8) were obtained under these conditions using cyclic secondary amines, such as morpholine **2a** or piperidine **2b**, as nucleophiles, starting from variously substituted 2-ynylamines (eq 1).[6]

Interestingly, the substrate conversion rate and product yields were only slightly lower when the substrate to catalyst ratio was raised to 300, as exemplified by the results reported in entry 9 (to be compared with entry 1).

The reaction was slower using less nucleophilic acyclic secondary amines, such as diethylamine **2c**.[7] Thus, the reaction of **1a** with **2c**, carried out with a **1a**/PdI_2 molar ratio of 50 rather than 100, led, after 24 h, to the corresponding oxazolidinone **3ac** in 67% isolated yield at 75% substrate conversion (entry 10). Substrate conversion and product isolated yield reached 100% and 79%, respectively, after 48 h (entry 11 and eq 1). Similar results were obtained starting from **1b** (entry 12 and eq 1).



aa R_2NH = morpholine, R^1=Bn, R^2=R^3=Me: 94%
ba R_2NH = morpholine, R^1=Bn, R^2=Et, R^3=Me: 90%
ca R_2NH = morpholine, R^1=Bn, R^2-R^3=$(CH_2)_5$: 95%
da R_2NH = morpholine, R^1=Bu, R^2=Et, R^3=Me: 88%
ea R_2NH = morpholine, R^1=Bu, R^2-R^3=$(CH_2)_5$: 89%
fa R_2NH = morpholine, R^1=Bn, R^2=Me, R^3=Ph: 94%
ab R_2NH = piperidine, R^1=Bn, R^2=R^3=Me: 80%
bb R_2NH = piperidine, R^1=Bn, R^2=Et, R^3=Me: 83%
ac R_2NH = Et_2NH, R^1=Bn, R^2=R^3=Me: 79%
bc R_2NH = Et_2NH, R^1=Bn, R^2=Et, R^3=Me: 75%

Formation of the oxazolidinone derivative **3** can be rationalized as shown in Scheme 2 (anionic iodide ligands

(4) We have recently reported the synthesis of 4,4-dialkyl-5-[(methoxycarbonyl)methylene]oxazolidin-2-ones by Pd-catalyzed sequential oxidative carboxylation-methoxycarbonylation of α,α-dialkyl substituted 2-ynylamines: (a) Bacchi, A.; Chiusoli, G. P.; Costa, M.; Gabriele, B.; Righi, C.; Salerno, G. *Chem. Commun.* **1997**, 1209−1210. (b) Chiusoli, G. P.; Costa, M.; Gabriele, B.; Salerno, G. *J. Mol. Catal. A: Chem.* **1999**, *143*, 297−310. In that reaction, carbon dioxide was incorporated into the cycle, while carbon monoxide was incorporated into the (methoxycarbonyl)methylene moiety, so the process was completely different from that described in the present work, in which both the carbonyl groups present in the final product derive from carbon monoxide. The direct formation of 5-methylene-2-oxazolidinones by carboxylation of 2-ynylamines has also been reported; see, for example: (c) Costa, M.; Chiusoli, G. P.; Taffurelli, D.; Dalmonego, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1541−1546. (d) Maggi, R.; Bertolotti, C.; Orlandini, E.; Oro, C.; Sartori, G.; Selva, M. *Tetrahedron Lett.* **2007**, *48*, 2131−2134.

(5) For recent reviews on sequential catalysis, see: (a) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001−1020. (b) Lee, J. M.; Na, J.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302−312. (c) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365−2379. See also: (d) *Multimetallic Catalysis in Organic Synthesis*; Shibasaki, M., Yamamoto, Y., Eds.; Wiley-VCH: Weinheim, 2004; pp 46−48. For another recently reported example of sequential catalysis involving PdI_2, see: (e) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *Adv. Synth. Catal.* **2006**, *348*, 1101−1109. (f) Gabriele, B.; Mancuso, R.; Salerno, G.; Veltri, L. *Chem. Commun.* **2005**, 271−273.

(6) In a typical experiment, a 250 mL stainless steel autoclave was charged with PdI_2 (15.0 mg, 4.2×10^{-2} mmol), KI (70.0 mg, 0.42 mmol), and a solution of **1** (4.2 mmol) and the amine **2** (21.0 mmol) in DME (8.4 mL). Water (380 mL, 21.1 mmol) was then added, and the autoclave was sealed. While the mixture was stirred, the autoclave was charged with CO (16 atm) and air (up to 20 atm), and then heated at 100 °C with stirring for the required time. After cooling, the autoclave was degassed and opened. The solvent was evaporated, and the products were purified by column chromatography on neutral alumina using suitable hexane−AcOEt mixtures as eluent (see the Supporting Information for further details).

(7) Primary amines afforded the corresponding symmetrical ureas, according to a reactivity that we have already reported: Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* **2004**, *69*, 4741−4750.

Table 1. Synthesis of 5-(Carbamoylmethylene)oxazolidin-2-ones **3** by Sequential Pd-Catalyzed Oxidative Aminocarbonylation−Cyclocarbonylation of 2-Ynylamines **1**[a]

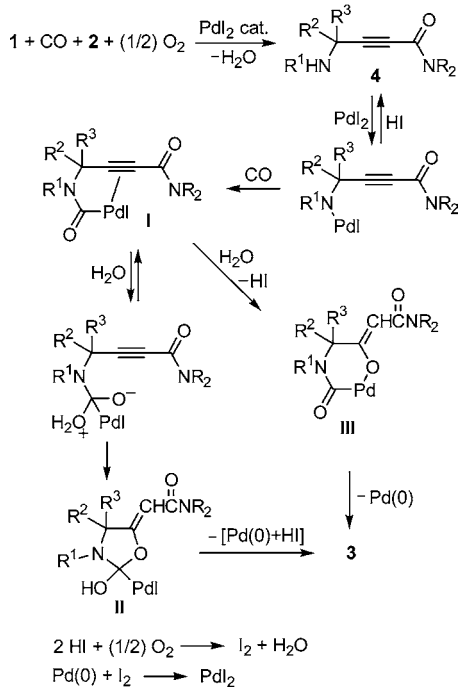
entry	**1**	R^1	R^2	R^3	**2**	R_2NH	PdI_2/KI/**1**/**2**/H_2O molar ratio	time (h)	**3**	yield of **3**[b] (%)
1	**1a**	Bn	Me	Me	**2a**	morpholine	1:10:100:500:500	5	**3aa**	98 (94)[c]
2	**1b**	Bn	Et	Me	**2a**	morpholine	1:10:100:500:500	5	**3ba**	96 (90)[d]
3	**1c**	Bn	$-(CH_2)_5-$		**2a**	morpholine	1:10:100:500:500	5	**3ca**	98 (95)[e]
4	**1d**	Bu	Et	Me	**2a**	morpholine	1:10:100:500:500	5	**3da**	92 (88)[c]
5	**1e**	Bu	$-(CH_2)_5-$		**2a**	morpholine	1:10:100:500:500	5	**3ea**	92 (89)[f]
6	**1f**	Bn	Me	Ph	**2a**	morpholine	1:10:100:500:500	5	**3fa**	97 (94)[c]
7	**1a**	Bn	Me	Me	**2b**	piperidine	1:10:100:500:500	6	**3ab**	84 (80)[g]
8	**1b**	Bn	Et	Me	**2b**	piperidine	1:10:100:500:500	6	**3bb**	88 (83)[g]
9	**1a**	Bn	Me	Me	**2b**	morpholine	1:10:300:1500:1500	8	**3aa**	84 (80)[e]
10[h]	**1a**	Bn	Me	Me	**2a**	Et_2NH	1:10:50:250:250	24	**3ac**	70 (67)[f]
11	**1a**	Bn	Me	Me	**2c**	Et_2NH	1:10:50:250:250	48	**3ac**	83 (79)[f]
12	**1b**	Bn	Et	Me	**2c**	Et_2NH	1:10:50:250:250	48	**3bc**	80 (75)[i]

[a] Unless otherwise noted, all reactions were carried out in DME (0.5 mmol of **1**/mL of DME, 4 mmol scale based on **1**) at 100 °C under 20 atm (at 25 °C) of a 4:1 mixture of CO−air in the presence of PdI_2, KI, a secondary amine **2**, and H_2O. Unless otherwise noted, substrate conversion was quantitative in all cases. [b] GLC yield (isolated yield) based on **1**. [c] $Z/E = 2.8$. [d] $Z/E = 2.5$. [e] $Z/E = 2.2$. [f] $Z/E = 3.0$. [g] $Z/E = 2.6$. [h] Substrate conversion was 75%. [i] $Z/E = 2.9$.

are omitted for clarity). The first process corresponds to oxidative aminocarbonylation of the triple bond of **1** to give the 2-ynamide intermediate **4**, according to a reactivity that we disclosed some years ago in the case of simple 1-alkynes.[8] In agreement with this hypothesis, no reaction occurred starting from 2-ynylamines bearing an internal triple bond, which clearly cannot undergo this kind of reaction.

Intermediate **4** is then converted into the carbamoylpalladium complex **I** through the reaction of the amino group with PdI_2 followed by CO insertion. Attack by water to the carbonyl of **I** followed by intramolecular conjugate addition then gives intermediate **II**. Elimination of [Pd(0) + HI] from the H−O−C−Pd-I unit of **II** eventually affords **3**. Alternatively, water addition to the coordinated triple bond of **I** can take place to give palladacycle derivative **III**. Reductive elimination eventually leads to the final product **3** and Pd(0). In any case, Pd(0) is then reoxidized according to the mechanism we disclosed some years ago,[9] involving oxidation of HI to I_2 followed by oxidative addition of the latter to Pd(0). Thus, formation of **3** from **1** takes place through the concatenation of two catalytic cycles, both promoted by PdI_2: oxidative aminocarbonylation of the triple bond to give **4** followed by oxidative water-driven cyclocarbonylation (Scheme 1).

Scheme 2



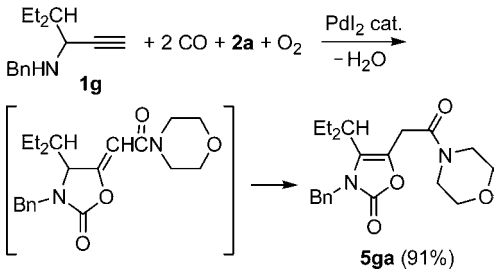
According to the mechanistic hypothesis shown in Scheme 2, a key step in the formation of **3** is represented by the nucleophilic attack by water on intermediate **I** to give complexes **II** or **III**. Thus, water is expected to play an essential role in the catalytic process. This has been confirmed by carrying out the same reaction reported in entry 5 but in the absence of added water and in the presence of molecular sieves 4A: after 5 h reaction time, the substrate conversion was only 50%, 2-oxazolidinone **3ea** ($Z/E = 1.75$) being formed in 22% isolated yield. Interestingly, the formation of 2-ynamide **4ea** (21% isolated yield) was also observed under these conditions. In agreement with our mechanistic hypothesis, **4ea** was quantitatively converted into **3ea** ($Z/E = 2.3$) under the conditions of entry 5. This result further confirms that 2-ynamides **4** are the intermediates in the formation of oxazolidinones **3**.

Interestingly, in the case of an α-monosubstituted propargylamine, such as benzyl-[1-(1-ethylpropyl)prop-2-ynyl]-amine **1g**, under the same conditions of entry 1, the initially formed oxazolidinone derivative spontaneously underwent shift of the double bond into the cycle with formation of a

(8) Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M. *J. Organomet. Chem.* **2001**, *622*, 84−88.
(9) Gabriele, B., Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 83−87.

3*H*-oxazol-2-one derivative **5ga** in excellent yield (96% GLC yield, 91% isolated) (Scheme 3).[10]

Scheme 3



In conclusion, we have reported an innovative method for the one-step synthesis of 2-oxazolidinone derivatives **3** starting from α,α-disubstituted 2-ynylamines **1**, via an unprecedented concatenation of two catalytic cycles, both promoted by PdI_2, corresponding to oxidative aminocarbonylation of the triple bond followed by water-driven oxidative cyclocarbonylation. In the case of an α-monosubstituted 2-ynylamine, such as **1g**, the initially formed oxazolidinone derivative spontaneously underwent shift of the double bond into the cycle with formation of a 3*H*-oxazol-2-one derivative **5ga**. All products have been obtained in good to excellent isolated yields under relatively mild conditions.

(10) The reaction of simple, unsubstituted benzylprop-2-ynylamine led to a complex mixture of unidentified, chromatographically immobile materials.

Acknowledgment. Thanks are due to the Consorzio Interuniversitario Nazionale "Metodologie e Processi Innovativi di Sintesi" (CINMPIS) (Bari, Italy) for a grant to P.P.

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

OL071332C