ORGANIC LETTERS

2008
Vol. 10, No. 7
1357−1359

Synthesis of Morpholin-2-ones by Chemoselective Intramolecular Rhodium-Catalyzed Reductive Ring Expansion of Oxazolidines

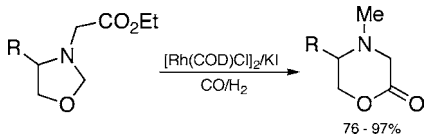
Maksym Vasylyev and Howard Alper*

Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

howard.alper@uottawa.ca

Received December 31, 2007

ABSTRACT



The rhodium-catalyzed reductive intramolecular ring expansion of *N*-(ethoxycarboxymethyl)oxazolidines was carried out under an atmosphere of carbon monoxide and hydrogen to afford *N*-methylmorpholin-2-ones in good to excellent yields.

The traditional approach to the synthesis of the majority of heterocyclic compounds involves the use of appropriate alicyclic precursor(s) that lead to the formation of the desirable heterocycle upon cyclization reaction. Although this approach is widely applied, an alternative strategy, which takes advantage of the fact that some heterocyclic compounds can be prepared from smaller heterocyclic substrates by the transition metal-catalyzed ring expansion process, has attracted a great deal of attention in the last 20 years.[1]

The most extensively investigated example of the ring expansion strategy is the insertion of carbon monoxide into a carbon-heteroatom bond of a heterocyclic compound.[1] The reaction proceeds well for three- and four-membered heterocycles since the ring-opening and expansion can be facilitated by relief of ring strain during the transformation. As a result, the synthesis of β-lactams, β-lactones, γ-lactones, and their thio analogues by the ring-expansion carbonylation reaction has been extensively studied.[2] Electrophiles other than carbon monoxide such as isocyanates, isothiocyanates and carbodiimides were also used for the ring-expansion reaction, thus significantly broadening the scope of the target products.[3]

The carbonylative ring expansion of five-membered ring heterocycles usually proceeds under more drastic conditions (higher temperatures and pressures of CO) than those required for smaller heterocycles.[1a] In some instances, as was demonstrated by one of us earlier in the case of thiazolidines, the reaction product was not the expected thiomorpholinone, but instead, was a thiazolidinone, formed as a result of a sequential carbonylation−ketene extrusion−carbonylation process.[4] The ring expansion−contraction of thiazolidines

(1) Khumtaveeporn, K.; Alper, H. *Acc. Chem. Res.* **1995**, *28*, 414−422. (b) Church, T. L.; Getzler, Y. D. Y. L.; Bryne C. M.; Coates G. W. *Chem. Commun.* **2007**, 657−674.

(2) (a) Heck, R. F. *J. Am. Chem. Soc.* **1963**, *85*, 1460−1463. (b) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931−934. (c) Kamiya, Y.; Kawato, K.; Ota, H. *Chem. Lett.* **1980**, 1549−52. (d) Lee, J. T.; Thomas, P. J.; Alper, H. *J. Org. Chem.* **2001**, *66*, 5424−5426. (e) Lu, S.; Alper, H. *J. Org. Chem.* **2004**, *69*, 3558−3561. (f) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2781−2784. (g) Rowley, J. M.; Lobkovsky, E. B.; Coates, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 4948−4960. (h) Piotti, M. E.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 111−116. (i) Shimizu, I.; Maruyama, T.; Makuta, T.; Yamamoto, A. *Tetrahedron Lett.* **1993**, *34*, 2135−2138. (j) Tanner, D.; Somfai, P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2415−2418. (k) Wang, M. D.; Calet, S.; Alper, H. *J. Org. Chem.* **1989**, *54*, 20−21.

(3) (a) Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887−5890. (b) Inman, G. A.; Butler, D. C. D.; Alper, H *Synlett* **2001**, 914−919. (c) Larksarp, C.; Sellier, O.; Alper, H. *J. Org. Chem.* **2001**, *66*, 3502−3506. (d) Church, T. L.; Byrne, C. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 8156−8162.

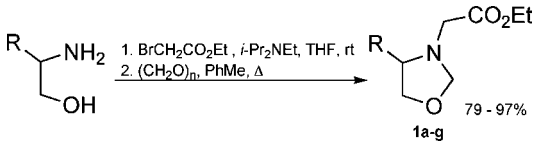
10.1021/ol703135w CCC: $40.75
Published on Web 03/01/2008

led us to investigate the reactivity of the structurally related *N*-(ethoxycarboxymethyl)oxazolidines under similar reaction conditions.

We now describe the synthesis of new *N*-(ethoxycarboxymethyl)oxazolidines and their reaction with the [Rh(COD)Cl]$_2$/KI catalytic system under carbonylative conditions. We further show that the reactivity of the *N*-(ethoxycarboxymethyl)oxazolidines differs significantly from their thioanalog in that instead of ring expansion-contraction, it undergoes intramolecular reductive ring expansion with the formation of morpholin-2-ones. This approach constitutes a new route to these particular types of heterocycles.[5]

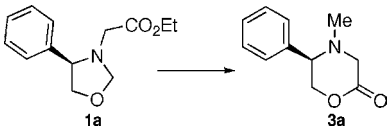
Substituted *N*-(ethoxycarboxymethyl)oxazolidines were synthesized starting from the corresponding enantiomerically pure amino alcohols[6] by alkylation with ethyl bromoacetate and subsequent cyclization with paraformaldehyde,[7] attaining the desired oxazolidines as depicted in Scheme 1.

Scheme 1. Synthesis of *N*-(Ethoxycarboxymethyl)oxazolidines



An initial attempt employing **1a** as a model substrate and 5 mol % of [Rh(COD)Cl]$_2$ and 10 mol % of KI as the catalyst, in toluene at 180 °C under 65 atm of carbon monoxide, gave only 11% of the reaction product which appeared to be (5*R*)-4-*N*-methyl-5-phenylmorpholin-2-one **3a** (Table 1, entry 1). In the absence of the catalyst, or using

Table 1. Catalytic Reductive Ring Expansion of **1a**[a]



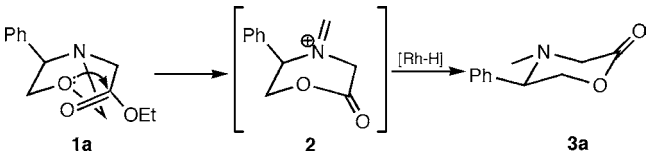
entry	catalyst[b]	CO, atm	H_2, atm	*t*, °C	yield,[c] %
1	[Rh(COD)Cl]$_2$/KI	65		180	11
2	[Rh(COD)Cl]$_2$/KI	30	30	180	95
3		65		180	*d*
4	$Co_2(CO)_8$/$Ru_3(CO)_{12}$	50		180	*d*
5	[Rh(COD)Cl]$_2$/KI		30	100	*e*
6	[Rh(COD)Cl]$_2$/KI	30	30	100	97
7	[Rh(COD)Cl]$_2$/KI	5	5	100	97

[a] All experiments were carried out in anhydrous toluene for 15 h. [b] Entries 1, 2, 5−7: [Rh(COD)Cl]$_2$, 5 mol %, KI, 10 mol %; entry 4: $Co_2(CO)_8$, 30 mol %, $Ru_3(CO)_{12}$, 14 mol %. [c] Isolated yield after purification by column chromatography. [d] Starting material was decomposed. [e] Rhodium metal deposition was observed.

$Co_2(CO)_8$/$Ru_3(CO)_{12}$ as the catalytic system, reaction resulted in the formation of decomposition products (Table 1, entries 3 and 4).

Isolation of (5*R*)-4-*N*-methyl-5-phenylmorpholin-2-one **3a** suggested that the ring expansion did take place. However, spectroscopic evidence indicated the absence of the ethoxycarboxymethyl fragment and the presence of the methyl group attached to the nitrogen atom, thus leading us to conclude that the ring expansion did not happen through the ring expansion−carbonylation sequence. Rather, it may have proceeded through an intramolecular nucleophilic attack of the oxygen atom of the oxazolidine at the carbon of the ester functional group, resulting in the formation of iminium intermediate **2** as illustrated in Scheme 2.

Scheme 2. Proposed Mechanism for the Intramolecular Ring Expansion of **1a** via the Intermediate Iminium Ion **2**



The next step in the reaction is most likely a two-electron one-proton reduction (formal hydride addition) of **2**. Although it is not clear how this step occurred since there was no source of hydride in the reaction media, we rationalized that the conversion could be improved by the use of a mixture of carbon monoxide and hydrogen instead of pure carbon monoxide to satisfy the need for the rhodium hydride species in the reaction. As illustrated in Table 1 (entry 2), the use of CO/H_2 mixture dramatically improves the conversion of **1a** into (5*R*)-4-*N*-methyl-5-phenylmorpholin-2-one **3a** affording the product in nearly quantitative yield. Additional evidence for our mechanistic hypothesis was obtained by carrying the reaction out under an atmosphere of deuterium gas and carbon monoxide. The ^{13}C NMR spectrum of the isolated compound shows a signal for the carbon nucleus of the *N*-methyl functional group as a triplet due to carbon-deuterium coupling.[8] The use of pure hydrogen gas (no CO), however, results in a reduction of the rhodium catalyst and deposition of rhodium metal in the form of "rhodium mirror" (Table 1, entry 5). It is evident, therefore, that although carbon monoxide does not participate in the reaction directly, its presence is necessary to stabilize the catalyst.

Further optimization showed that the reaction temperature could be decreased from 180 to 100 °C (Table 1, entry 6),

(4) Khumtaveeporn, K.; Alper, H. *J. Am. Chem. Soc.* **1994**, *116*, 5662−6.

(5) Alternative routes to (5*R*)-4-*N*-methyl-5-phenylmorpholin-2-one **3a** were described in following articles: (a) Alker, D.; Harwood, L. M.; Williams, C. E. *Tetrahedron* **1997**, *53*, 12671−12678. (b) Agami, C.; Couty, F.; Hamon, L.; Prince, B.; Puchot, C. *Tetrahedron* **1990**, *46*, 7003−7010. (c) Agami, C.; Couty, F.; Daran, J. C.; Prince, B.; Puchot, C. *Tetrahedron Lett.* **1990**, *31*, 2889−2892.

(6) McKennon, J. M.; Meyers A. I. *J. Org. Chem.* **1993**, *58*, 3568−3571.

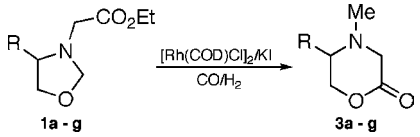
(7) Compounds **1a** and *N*-(cyanomethyl)-4-phenyloxazolidine: Deprez, P.; Royer, J.; Husson, H.-P. *Tetrahedron* **1993**, *49*, 3781−3792.

(8) The fact that only 63% of the compound has N-CH_2D structural fragment (calculated according to the integral values of the NMR spectrum, (S11 (inset), Supporting Information) may be due to hydrogen-deuterium exchange which occurs in rhodium hydride bonded to 1,5-cyclooctadiene.

and the pressure of hydrogen and carbon monoxide could be reduced to 5 atm (Table 1, entry 7).

With these optimized conditions in hand, the scope of the rhodium-catalyzed reductive intramolecular ring expansion of *N*-(ethoxycarboxymethyl)oxazolidines was examined. The results summarized in Table 2 demonstrate that the catalytic

Table 2. Catalytic Reductive Intramolecular Ring Expansion of *N*-(Ethoxycarboxymethyl)oxazolidines[a,9]



entry	compd	R	yield,[b] %
1	**3a**	(*R*)-Ph	97
2	**3b**	(*S*)-Ph	80
3	**3c**	(*R*)-*i*-Bu	95
4	**3d**	(*S*)-*i*-Bu	81
5	**3e**	(*R*)-Bn	97
6	**3f**	(*S*)-Bn	81
7	**3g**	(*S*)-*i*-Pr	76

[a] Reaction conditions: $[Rh(COD)Cl]_2$, 5 mol %, KI, 10 mol %, CO, 5 atm, H_2, 5 atm, toluene, 10 mL, 100 °C, 15 h. [b] Isolated yield after purification by column chromatography.

reductive ring expansion of oxazolidines **1a**−**g** provides *N*-methylmorpholin-2-ones **3a**−**g** in good to excellent yields. Neither the nature, nor the stereo configuration of the substituent at position 4 of the oxazolidine ring, has a significant influence on the performance of the reaction.

To probe whether the reductive ring expansion reaction could be extended to substrates containing an *N*-cyanomethyl substituent, *N*-(cyanomethyl)-4-phenyloxazolidine[7] was synthesized. Unfortunately, no morpholin-2-imine was formed during the reaction conducted using conditions suitable for ring expansion of *N*-(ethoxycarboxymethyl)oxazolidines.

In conclusion, we have developed a rhodium-catalyzed method for the novel reductive ring expansion of *N*-(ethoxycarboxymethyl)oxazolidines to *N*-methylmorpholin-2-ones. The reaction may proceed through an intermediate iminium ion, which undergoes further reduction by a rhodium hydride species.

Acknowledgment. We are grateful to the National Science and Energy Research Council of Canada for support of the research.

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

OL703135W

(9) General procedure for the catalytic ring expansion reaction: In a typical procedure, 1 mmol of *N*-(ethoxycarboxymethyl)oxazolidine and 0.05 mmol of $[Rh(COD)Cl]_2$ were dissolved in 10 mL of anhydrous toluene in a glass liner equipped with a magnetic stirring bar. To this solution was added 0.1 mmol of KI, and the liner was inserted into a 45 mL autoclave, which was then sealed. Carbon monoxide, 5 atm, was introduced to the autoclave by the two consecutive pump-release cycles. Finally, hydrogen gas was introduced into the autoclave bringing the overall pressure to 10 atm. The autoclave was placed in a thermostated oil bath at 100 °C and the reaction was carried out for 15 h. The autoclave was then cooled, and pressure was released. The reaction mixture was concentrated, and the residue was subjected to flash chromatography.