ORGANIC LETTERS

2007
Vol. 9, No. 8
1485−1488

Domino Metathesis of 3,6-Dihydro-1,2-oxazine: Access to Isoxazolo[2,3-*a*]pyridin-7-ones

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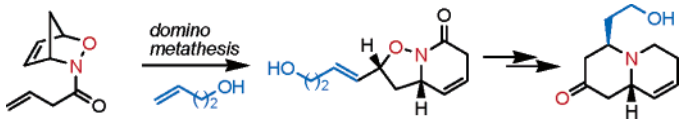
Received January 26, 2007

ABSTRACT

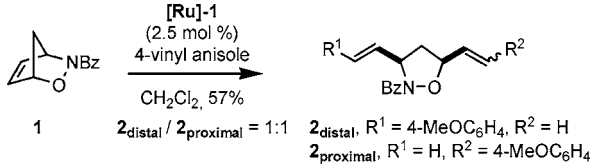


Strained bicyclic 3,6-dihydro-1,2-oxazine is a reactive substrate in domino metathesis with an external alkene. This general transformation leads to isoxazolo[2,3-*a*]pyridin-7-one, a versatile scaffold combining chemical functions that could be selectively oxidized or reduced. The synthetic relevance of these domino metathesis products is demonstrated by a straightforward synthesis of a quinolizinone.

[4 + 2] Cycloaddition reactions create two bonds simultaneously and up to four stereogenic centers. A rapidly expanding area, the nitroso Diels−Alder reaction,[1] allows the straightforward synthesis of 3,6-dihydro-1,2-oxazines. These versatile scaffolds can be viewed as latent 1,4-*cis* aminoalcohols, piperidines, or pyrroles (for example).[2,3] Recent progress from Yamamoto's group has extended this [4 + 2] cycloaddition to the first catalytic and enantioselective version.[4] We have recently reported the use of α-acetoxy nitroso as a reactive dienophile in [4 + 2] cycloaddition reaction.[5,6] In line with our studies on the reactivity of these new nitroso dienophiles and their potential synthetic applications,[3c] we report herein our studies on the domino metathesis reaction of strained bicyclic 3,6-dihydro-1,2-oxazine catalyzed by ruthenium alkylidene.

Pioneering studies by King have shown that ROCM of strained [2.2.1] bicyclic dihydrooxazine **1** led to a 1:1 mixture of regioisomeric isoxazolidines **2** in 57% yield (*E*/*Z* = 1:1, Scheme 1).[7] However, to the best of our knowledge the domino metathesis of nitroso Diels−Alder cycloadducts has not been disclosed in the literature. Domino metathesis has

Scheme 1



1 **2**$_{distal}$ / **2**$_{proximal}$ = 1:1 **2**$_{distal}$, R^1 = 4-MeOC$_6$H$_4$, R^2 = H; **2**$_{proximal}$, R^1 = H, R^2 = 4-MeOC$_6$H$_4$

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(1) (a) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: New York, 1991. (b) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317−1348. (c) Leach, A. G.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 5192−5200.

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(3) (a) Kresze, G.; Haertner, H. J. *Liebigs Ann. Chem.* **1973**, *4*, 650−658. (b) Givens, R. S.; Choo, D. J.; Merchant, S. N.; Stitt, R. P.; Matuszewski, B. *Tetrahedron Lett.* **1982**, *23*, 1327−1330. (c) Calvet, G.; Blanchard, N.; Kouklovsky, C. *Synthesis* **2005**, 3346−3354.

(4) (a) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514−3525. (b) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031−2043.

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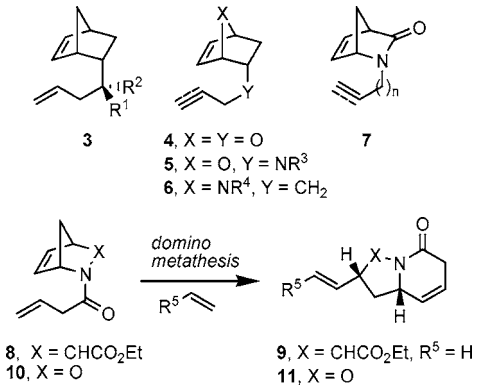
10.1021/ol0702066 CCC: $37.00
Published on Web 03/13/2007

been under close scrutiny in the past few years.[8] This reaction uses favorable thermodynamics to rearrange a (strained) unsaturated bicycle in the presence of a catalytic amount of a ruthenium carbene. Several bicyclic systems have been evaluated in this domino transformation, including bicyclo-[2.2.1]heptenes **3**,[9] oxa-[9c,10] or azabicyclo[2.2.1]heptenes **4**−**6**,[9c,10a,11] and 2-azabicyclo[2.2.1]hept-5-en-3-ones **7** (Scheme 2).[12] Recently, Maison et al. described a ring-opening/ring-

Scheme 2

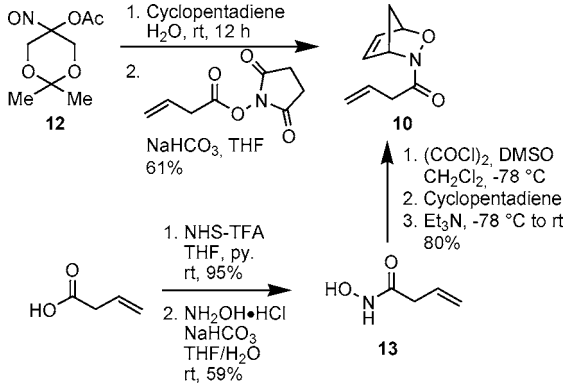


closing metathesis sequence from **8** (X = $CHCO_2Et$), leading to functionalized azabicycloalkane **9**.[13]

Starting from strained nitroso Diels−Alder adducts (**10**, X = O) and an alkene R^5CHCH_2, domino metathesis should allow direct access to rare scaffolds, isoxazolo[2,3-*a*]pyridin-7-ones **11**. The newly formed bicyclic derivatives **11** are very attractive because they combine chemical functions that could be oxidized (two easily differentiated carbon−carbon double bonds) or reduced (nitrogen−oxygen bond, lactam carbonyl). In addition, the two stereogenic centers would not be altered.[14] The substitution pattern of both the domino precursor **10** and the external alkene R^5CHCH_2 could also be varied at will, thus offering another possibility of chemical diversity. Eventually, this domino metathesis sequence could be synthetically useful in the multistep elaboration of biologically relevant targets. The isoxazolo[2,3-*a*]pyridin-7-ones are structural motifs shared by potent tyrosine kinase inhibitors such as pyridomacrolidin, a fungal metabolite isolated from *Beauvaria bassiana*.[15] The synthetic importance of this domino sequence will be illustrated in the last part of this communication.

To evaluate the domino metathesis of 3,6-dihydro-1,2-oxazine, we required in the first place an efficient synthetic procedure for the domino precursor **10** (Scheme 3). Aqueous

Scheme 3



[4 + 2] cycloaddition reaction of α-acetoxynitroso **12**[6] with cyclopentadiene in water at room temperature followed by acylation reaction afforded dihydrooxazine **10** in 61% yield. Alternatively, the bicyclic 3,6-dihydro-1,2-oxazine can be obtained in two steps from commercially available 3-butenoic acid. The latter was transformed into the corresponding hydroxamic acid **13** by hydroxaminolysis reaction (59%) of the corresponding activated ester.[16,17] Swern oxidation[18] followed by immediate trapping of the intermediate acyl-nitroso by cyclopentadiene led to the desired dihydrooxazine **10** (80%).[19]

Having a suitable access to compound **10**, we turned our attention to its reactivity in the presence of ruthenium carbenes (Scheme 4). Two precatalysts have been evaluated in this study, second generation Grubbs carbene[20] **[Ru]-2** and Hoveyda−Grubbs carbene[21] **[Ru]-3**.

Initial experiments were disappointing: no reaction occurred when strained 3,6-dihydro-1,2-oxazine **10** was treated with 5 mol % of **[Ru]-2** in refluxing methylene chloride. Ethylene pressure (up to 25 bar) was then applied to the reaction vessel, without success.[22] However, the addition of an external alkene such as allyltrimethylsilane dramatically

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(11) Liu, Z.; Rainier, J. D. *Org. Lett.* **2006**, *8*, 459−462.

(12) (a) Arjona, O.; Csákÿ, A. G.; Medel, R.; Plumet, J. *J. Org. Chem.* **2002**, *67*, 1380−1383. (b) Arjona, O.; Csáky, A. G.; León, V.; Medel, R.; Plumet, J. *Tetrahedron Lett.* **2004**, *45*, 565−567.

(13) Büchert, M.; Meinke, S.; Prenzel, A. H. G. P.; Deppermann, N.; Maison, W. *Org. Lett.* **2006**, *8*, 5553−5556.

(14) Racemic substrates were used in the present study. However, enantiomerically pure educts are available, see ref 1b.

(15) Rao Irlapati, N.; Baldwin, J. E.; Adlington, R. M.; Pritchard, G. J.; Cowley, A. R. *Tetrahedron* **2006**, *62*, 4603−4614.

(16) (a) Rajendra, G.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4471−4477. (b) Sakaibara, S.; Inukai, N. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1979−1984.

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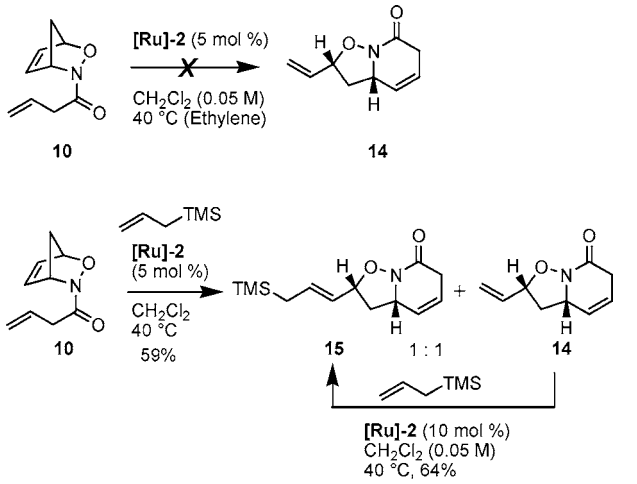
(18) Martin, S. F.; Hartmann, M.; Josey, J. A. *Tetrahedron Lett.* **1992**, *33*, 3583−3586.

(19) Periodate oxidants should be avoided in the oxidation reaction of hydroxamic acid **13** because they promote double-bond isomerization from the β,γ- to the α,β-position.

(20) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(21) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.

Scheme 4

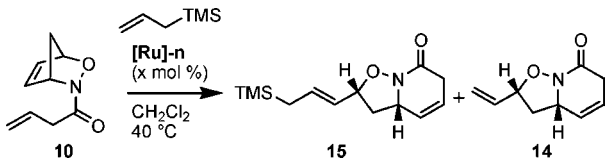


changed the reaction outcome. In 4 h, a 1:1 mixture of isoxazolo[2,3-*a*]pyridin-7-ones **15** (*E*/*Z* = 4:1) and **14** was obtained (59%) in refluxing CH_2Cl_2 (0.05 M).[23] The latter compound can be easily transformed into **15** by a cross-metathesis reaction with allyltrimethylsilane (10 mol % **[Ru]-2**, 64%).

Encouraged by this positive result, we tried to optimize the yield and product distribution of this domino metathesis (Table 1). Striking solvent concentration dependence was observed: when the reaction was run at 0.01 M in methylene chloride, the yield dropped to 30% (**15**/**14** = 80:20, Table 1, entry 1). However, at 0.05 M, the yield increased to 91% at the expense of the product distribution (**15**/**14** = 60:40, Table 1, entry 2). Keeping 0.05 M as an optimal concentration, we aimed at increasing the **15/14** ratio. The quantity of precatalyst was increased to 7.5 mol % (Table 1, entry 3), leading to a **15**/**14** ratio of 80:20 (86%). Identical results were obtained when carbene **[Ru]-2** was replaced by Hoveyda−Grubbs carbene **[Ru]-3** (Table 1, entry 3 vs entry 5). A further increase in precatalyst loading to 10 mol % (in two separate additions of 5 mol %) led to a ratio of 85:15 (93%, Table 1, entry 4). Such a dependence on concentration and catalyst loading has been recently observed by Maison et al. in related systems.[13]

With these optimum conditions in hand, we turned our attention to the generality of this domino sequence (Table 2). Different alkenes were then evaluated. Electron-deficient alkenes (such as 1-phenyl-propen-2-one, allylphenylsulfone)[24] or propargylic alcohol were unreactive cross-metathesis partners. In contrast, allylic alcohol led to a 55:45 mixture of **16a**/**14** in 75% yield (Table 2, entry 1). However, the yield and product distribution were not reproducible, probably as a result of competitive double bond isomerization processes.[25] Homoallylic and bishomoallylic alcohols were

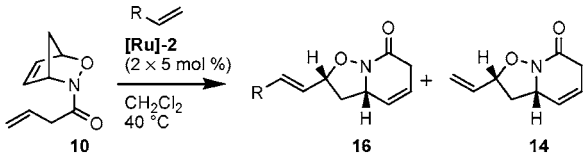
Table 1. Optimization of Reaction Conditions

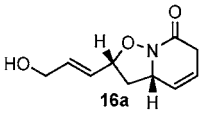
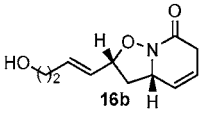
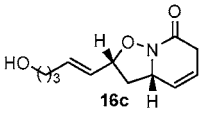
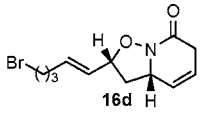
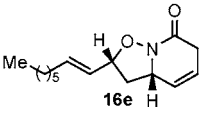


entry	catalyst	concn (M)	**15/14** ratio[a]	yield (%)[b]
1	**[Ru]-2**, 5 mol %	0.01	80:20	30
2	**[Ru]-2**, 5 mol %	0.05	60:40	91
3	**[Ru]-2**, 7.5 mol %	0.05	80:20	86
4	**[Ru]-2, 2 × 5 mol %**	**0.05**	**85:15**	**93**
5	**[Ru]-3**, 7.5 mol %	0.05	80:20	85

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Combined isolated yield.

Table 2. Scope of the Reaction



entry	alkene	product	**16/14** ratio[a]	yield (%)[b]
1		 **16a**	55 : 45	75[c]
2		 **16b**	90 : 10	87
3		 **16c**	96 : 4	91
4		 **16d**	80 : 20	86
5		 **16e**	60 : 40	85

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Combined isolated yield. [c] Not reproducible; see text.

(22) (a) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388−12389. (b) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082−6083. (c) Diver, S. T.; Giessert, A. J. *Synthesis* **2004**, 466−471. (d) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271−2274.

(23) The structures of compounds **15** and **21** have been determined by homo- and heteronuclear NMR experiments (HSQC, HMBC, NOESY).

(24) This low reactivity is in sharp contrast with literature data; see: Michrowska, A.; Bieniek, M.; Kim, M.; Klajn, R.; Grela, K. *Tetrahedron* **2003**, *59*, 4525−4531.

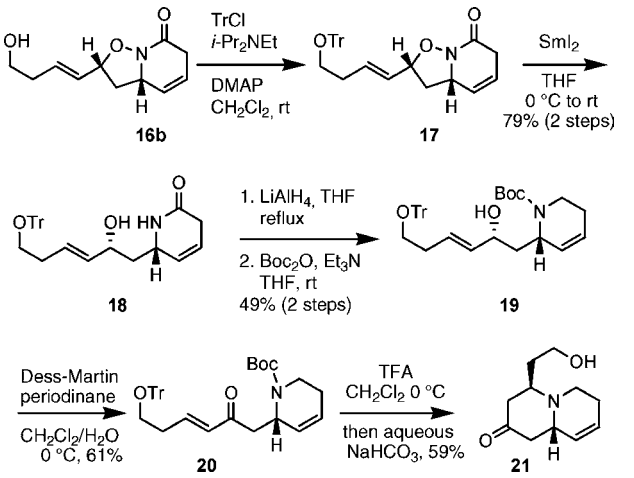
reliable partners in this domino sequence, leading to isoxazolo[2,3-*a*]pyridin-7-ones **16b** and **16c** (as a separable mixture with **14**) in 77% and 91% combined yield, respectively (Table 2, entries 2 and 3). 1-Octene or pent-4-enyl bromide led to good yields of the desired rearranged bicycles (Table 2, entries 4 and 5).

From a mechanistic point of view, the domino precursor **10** presents two independent sites of initiation for the ruthenium precatalyst: terminal double bond or internal unsaturation. No direct evidence in favor of one or the other pathway has been obtained during our studies. Traces of products derived from ring-opening/cross-metathesis could be observed when the reaction was conducted with allyltrimethylsilane as an external alkene. This experimental observation is indicative of the second pathway but does not rule out the first. The two pathways might be simultaneously operative.[8a]

The synthetic importance of the isoxazolo[2,3-*a*]pyridin-7-one scaffold has been demonstrated in a straightforward synthesis of the quinolizinone[26] moiety, the core structure of many biologically relevant alkaloids.[27]

The hydroxyl moiety of compound **16b** was protected as a trityl ether[28] and the N−O bond was cleaved using SmI_2 in THF (79%) (Scheme 5).[29] Upon reduction of the lactam function ($LiAlH_4$, THF) and protection of the resulting piperidine as a *tert*-butyl carbamate, compound **19** was obtained in 49% for two steps. Oxidation of the secondary alcohol with Dess−Martin periodinane led to the α,*β*-unsatured ketone **20** (61%).[30] Treatment of the latter with an excess of trifluoroacetic acid (CH_2Cl_2, 0 °C) followed by

Scheme 5



treatment with a saturated aqueous sodium bicarbonate solution triggered an intramolecular Michael addition, affording quinolizinone **21** in 59% yield.[23,31]

We have shown that properly substituted nitroso Diels−Alder cycloadducts can undergo domino metathesis with an external alkene in the presence of a catalytic quantity of ruthenium alkylidene. The isoxazolo[2,3-*a*]pyridin-7-ones thus obtained were shown to be synthetically useful in the multistep synthesis of biologically relevant alkaloids. Further efforts along these lines will be reported in due course.

Acknowledgment. We thank Professors Y. Langlois and J. Eustache and Drs. R. Lett and P. van de Weghe for fruitful discussions. Financial support from the CNRS and Université Paris XI is gratefully acknowledged.

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

OL0702066

(25) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414−7415.

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(27) Alternative strategies for the synthesis of similar nitrogen-containing heterocyles from 3,6-dihydro-1,2-oxazines have been reviewed, see ref 2.

(28) For an alternative synthetic scheme using silyl ether protection, see Supporting Information.

(29) Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995**, *36*, 7419−7422.

(30) Other oxidants were less effective in this transformation (IBX, 34%; TEMPO (10 mol %), $PhI(OAc)_2$, 55%).

(31) Zaja, M.; Blechert, S. *Tetrahedron* **2004**, *60*, 9629−9634.