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Molybdenum-Mediated Cleavage Reactions of Isoxazoline Rings Fused in Bicyclic Frameworks

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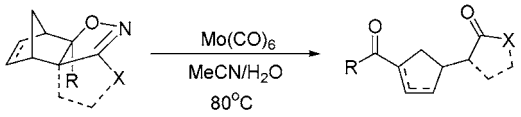
ABSTRACT

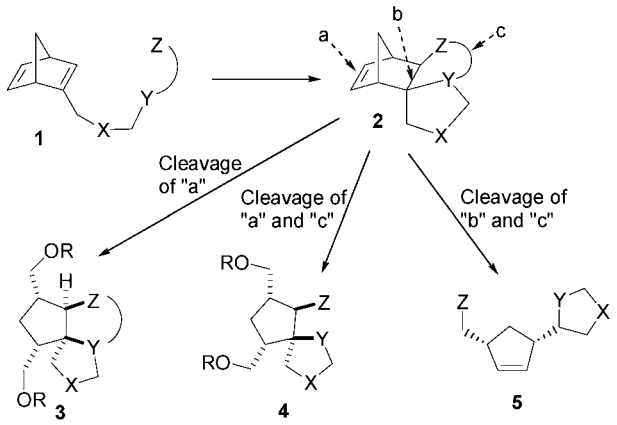


The molybdenum-mediated cleavage reactions of isoxazoline rings fused in bicyclic frameworks were investigated. A tandem N–O bond cleavage-retro aldol reaction of an isoxazoline ring fused in a bicyclic framework led to the cleavage of the bicyclic framework. These reactions provide a novel stereoselective synthesis of substituted cyclopentene rings, cyclopentane rings, and attached-ring systems.

Intramolecular cycloaddition reactions with high regio- and stereocontrol are among the most powerful methods for the efficient assembly of complex ring structures.[1] We have recently initiated a program on the study of various types of intramolecular cycloadditions of substituted norbornadienes.[2,3] Our long-term goal is to develop an efficient route for the construction of angular fused tricyclic frameworks (**3**), spirocyclic frameworks (**4**), and attached-ring frameworks (**5**) with high regio- and stereocontrol (Scheme 1).

Our recent investigation on the intramolecular 1,3-dipolar cycloadditions of norbornadiene-tethered nitrile oxides[2] and nitrones[3] have shown that although as many as eight different cycloadducts could be formed in these cycloadditions, most of these cycloadditions were found to be highly regio- and stereoselective, giving single cycloadducts in good yields (Scheme 2). In this paper, we report our initial results on the molybdenum-mediated cleavage reactions of cycloadducts **8** and related compounds, which provide a new strategy for the efficient assembly of attached-ring structures (rings linked by a C−C σ-bond). Since biologically active natural products containing attached-ring structures are widespread, for example, azadirachtin,[4] trichodiene and related com-

Scheme 1. Intramolecular Cycloaddition-Cleavage Approach to the Synthesis of Tricyclic, Spirocyclic, and Attached Rings



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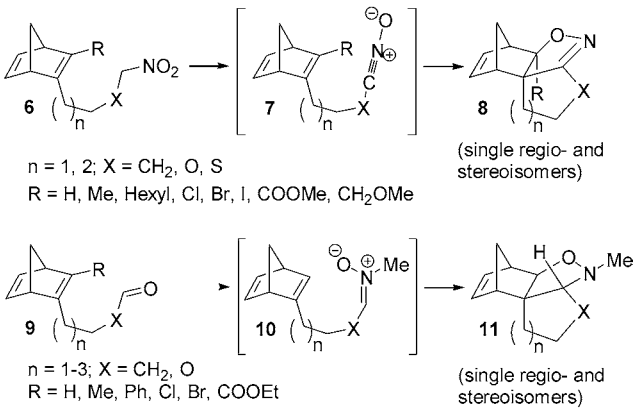
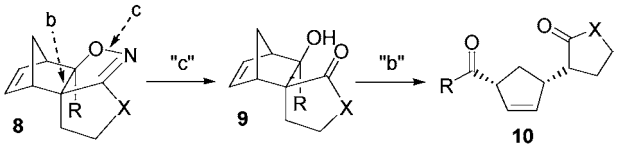
Scheme 2. Intramolecular 1,3-Dipolar Cycloadditions of Norbornadiene-Tethered Nitrile Oxides and Nitrones



pounds,[5] cuprenene,[6] manoalide,[7] fomannosin,[8] and isocaespitol,[9] development of novel and efficient methods for the construction of the attached-ring structures is valuable.[10]

There are several methods available for the cleavage of the N−O bond in an isoxazoline ring,[11] and the most common ones include catalytic hydrogenation over Raney-Ni[12] or Pd;[13] reduction by Zn in acetic acid;[14] reduction by lithium aluminum hydride;[15] reduction promoted by $TiCl_3$;[16] oxidation with ozone;[17] by treatment of $Mo(CO)_6$;[18] and reduction by SmI_2.[19] Our original plan for the conversion of cycloadduct **8** to the attached ring structure **10** involves a two-step procedure (Scheme 3): (i) cleavage of the N−O

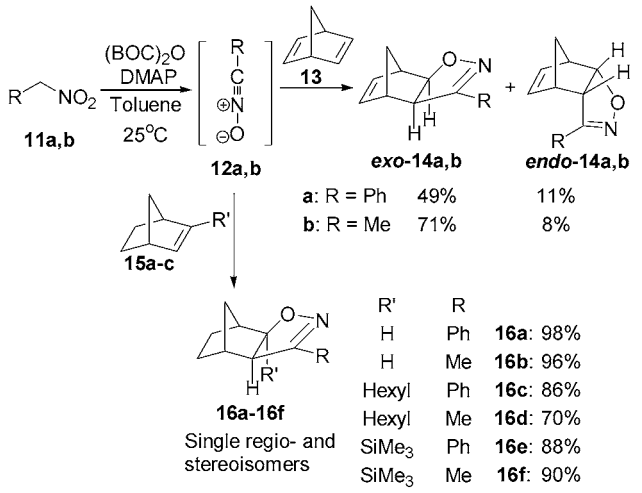
Scheme 3. Sequential Cleavage of Bond "C" and Bond "B" of **8**



bond in the isoxazoline ring in **8** (cleavage of bond "c") and (ii) a retro-aldol cleavage of bond "b" in the β-hydroxyketone **9**. To our delight, we found that treatment of cycloadducts **8** with $Mo(CO)_6$ led to the cleavage of both bond "b" and bond "c" in a *single-pot reaction*, providing the attached-ring structures **10** in moderate to good yields, vide infra.

To the best of our knowledge, there have been no previous studies on the Mo-mediated cleavage reactions of isoxazoline rings fused in a bicyclic framework reported in the literature. Initially we decided to begin our study on a simpler model system (**14a,b** and **16a-16f**, without the extra ring from the tether). The intermolecular cycloadducts **14a,b** and **16a−f** were prepared by the 1,3-dipolar cycloaddition of the corresponding bicyclic alkenes with the nitrile oxides **12a** and **12b** (generated from the corresponding nitroalkanes (**11a** and **11b**) using the Hassner $(BOC)_2O$/DMAP method, Scheme 4).[20,21] These 1,3-dipolar cycloadditions, which

Scheme 4. Intermolecular Nitrile Oxide Cycloadditions



occurred at room temperature using the Hassner $(BOC)_2O$/DMAP method, have a stereoselectivity (*exo* vs *endo*) much

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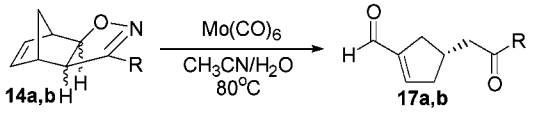
(21) For another novel method to generate nitrile oxides by dehydration of *O*-silylated hydroxamic acids, see: Muri, D.; Bode, J. W.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 539.

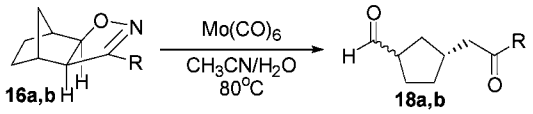
higher than those of the traditional Mukaiyama aromatic isocyanate method[22] or the Shimizu ethyl chloroformate method.[23] The cycloadditions of 2-substituted 2-norbornenes **15b** and **15c** were found to be completely regio- and stereoselective, giving single regio- and stereoisomers **16c**−**f** in good yields. Only the regioisomers with the oxygen of the nitrile oxide attached to C_2 of the norbornene were produced.[24]

The results of the Mo-mediated cleavage reactions of these intermolecular cycloadducts **14a,b** and **16a**−**f** are shown in Table 1. In the presence of 1 equiv of $Mo(CO)_6$ in

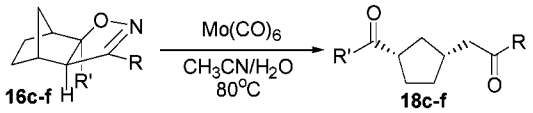
Table 1. Mo-Mediated Cleavage Reactions of Cycloadducts **14a,b** and **16a**−**f**



entry	cycloadduct	cleavage product	yield[a]
1	***exo*-14a**	**17a** (R=Ph)	66%
2	***endo*-14a**	**17a** (R=Ph)	70%
3	***exo*-14b**	**17b** (R=Me)	61%
4	***endo*-14b**	**17b** (R=Me)	62%



entry	cycloadduct	cleavage product	yield[a]
5	**16a**	**18a** (R=Ph)[b]	75%
6	**16b**	**18b** (R=Me)[c]	65%



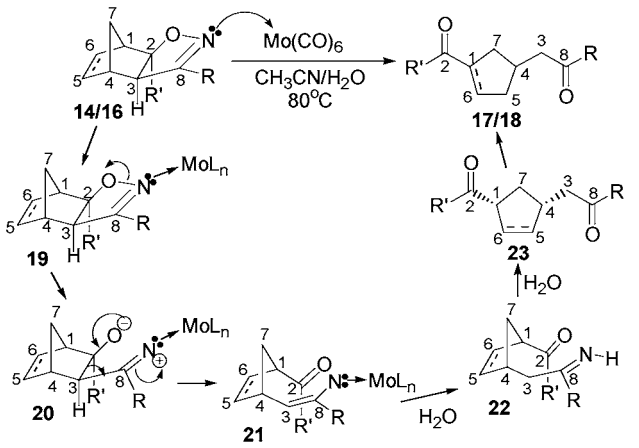
entry	cycloadduct	cleavage product	yield[a]
7	**16c**	**18c** (R'=Hexyl, R=Ph)[d]	75%
8	**16d**	**18d** (R'=Hexyl, R=Me)[d]	82%
9	**16e**	**18e** (R'=$SiMe_3$, R=Ph)[d]	65%
10	**16f**	**18f** (R'=$SiMe_3$, R=Me)[d]	84%

[a] Isolated yields after column chromatography. [b] As a 50:50 mixture of *cis* and *trans* isomers. [c] As a 60:40 mixture of *cis* and *trans* isomers. [d] As a single stereoisomer (*cis*).

acetonitrile/water at 80 °C, cycloadduct *exo*-**14a** (R = Ph) underwent a tandem reductive N−O bond cleavage-retroaldol reaction followed by isomerization of the double bond (all three steps occurred in one pot) to provide cyclopentane **17a** in 66% isolated yield (Table 1, entry 1). Under the same reaction conditions, the *endo*-cycloadduct *endo*-**14a** afforded an identical product (**17a**) in 70% yield (Table 1, entry 2). Similarly, Mo-mediated cleavage of cycloadducts *exo*-**14b** and *endo*-**14b** gave cyclopentene **17b** in 61% and 52% yield, respectively (Table 1, entries 3 and 4). Unlike the cycloadducts **16a** and **16b**, in which *cis* and *trans* mixtures of cyclopentane products **18a** and **18b** were formed (Table 1, entries 5 and 6),[25] Mo-mediated cleavage of cycloadducts **16c**−**f** afforded cyclopentanes as single stereoisomers, with a *cis* configuration (stereochemistry determined by GOESY NMR experiments),[26,27] in 65−82% yield (Table 1, entries 7−10).[28]

A possible mechanism for the tandem reductive N−O bond cleavage-retroaldol reaction of the cycloadducts **14** and **16** is outlined in Scheme 5. The nitrogen in the isoxazoline

Scheme 5. Possible Mechanism



ring coordinates to $Mo(CO)_6$ to give complex **19** and facilitate the N−O bond cleavage. Cleavage of the N−O bond leads to the formation of the nitrene complex **20**,[29] which undergoes retroaldol cleavage to give intermediate **21**. Hydrolysis of **21** would give **23** via the imine intermediate **22**. For the cycloadducts **14a/b**, the double bond in **23** isomerized to give the conjugated enones **17a/b**.

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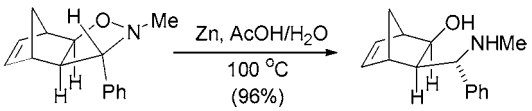
(25) No change in the ratio of the stereoisomers (50:50) of **18a** was observed upon treatment with KOH in $H_2O/CDCl_3$.
(26) For GOESY (gradient enhanced nuclear Overhauser enhancement spectroscopy), see: (a) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037. (b) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199. (c) Dixon, A. M.; Widmalm, G.; Bull, T. E. *J. Magn. Reson.* **2000**, *147*, 266.
(27) The structures of all cleavage products were determined by 1-D and 2-D NMR experiments: ^1H, ^{13}C (APT), HCOSY, HSQC and HMBC. HCOSY: $^1H-^1H$ correlated spectroscopy. HSQC: heteronuclear single quantum coherence. HMBC: heteronuclear multiple bond correlation. See: Crews, P.; Rodriguez, J.; Jaspars, M. *Organic Structure Analysis*; Oxford University Press: Oxford, 1998.
(28) Other than the Mo-mediated cleavage reactions, we have also attempted the cleavage reactions of these bicyclic nitrile oxide cycloadducts (**14** and **16**) using the more common reductive cleavage methods, such as Zn/AcOH, $LiAlH_4$, and Ra-Ni. Unfortunately in all of these cases, either starting materials were recovered or decomposition of the starting materials were observed. On the other hand, a bicyclic nitrone cycloadduct did undergo reductive cleavage using the Zn/AcOH method to provide the N−O bond cleavage product without undergoing a retroaldol cleavage:



(29) The coordination of the nitrogen with the Mo as well as the nitrene intermediate has previously been proposed by Baraldi and co-workers; see ref 18a.

While Mo-mediated cleavage of the cycloadducts **16a** and **16b** gave a mixture of stereoisomers (**18a/18b**), cycloadducts **16c**−**f** generated the cleavage products as single stereoisomers (*cis*) (**18c**−**f**, Table 1, entries 5 and 6 vs 7−10). There are two possible explanations. In the cyclopentane **23** (Scheme 5), the proton at C_1 is more acidic with R′ = H (i.e., an aldehyde group attached to C_1, **18a** and **18b**) than with R′ ≠ H (i.e., a ketone group attached to C_1, **18c**−**f**), and this more acidic proton epimerized under the reaction conditions.[30] Another possibility is that the bulkier ketone group prefers the pseudoequatorial position to a greater extent than the small aldehyde group in the envelope form of the five-membered ring (both substituents at C_1 and C_3 will be pseudoequatorial when they are *cis* to each other).

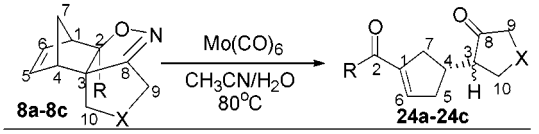
Since all the intermolecular nitrile oxide cycloadducts **14a/b** and **16a**−**f** underwent Mo-mediated tandem reductive N−O bond cleavage-retroaldol reactions to provide cyclopentane/cyclopentene rings, the intramolecular cycloadduct **8** (Scheme 3) should undergo a similar cleavage reaction to provide the attached-ring structure **10**. The results of the Mo-mediated cleavage reactions of the intramolecular cycloadduct **8a**−**e** are shown in Table 2.

Similar to the intermolecular cycloadducts, the intramolecular cycloadducts **8a**−**e** (Table 2) undergo tandem reductive N−O bond cleavage-retroaldol reactions in the presence of $Mo(CO)_6$, to provide attached-ring structures **24a**−**e** in moderate yields. Mo-mediated cleavage of the cycloadducts **8a**−**c** (with R = H) gave mixtures of two stereoisomers (at C_3, Table 2, entries 1−3), and the double bond at C_5−C_6 isomerized to C_1−C_6 to give the conjugated aldehydes **24a**−**c**. On the other hand, Mo-mediated cleavage of the cycloadducts **8d** and **8e** (with R ≠ H) occurred with no isomerization of the double bond (remained at C_5−C_6) to give cleavage products **24d** (as a 60:40 mixture of stereoisomers at C_3) and cleavage products **24e** (as a ∼42:39:14:5 mixture of stereoisomers at C_1 and C_3).

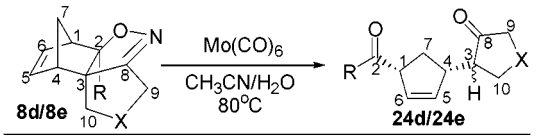
In conclusion, we have demonstrated the first examples of Mo-mediated tandem reductive N−O bond cleavage-retroaldol reactions of isoxazoline rings fused in bicyclic frameworks. This cycloaddition-cleavage protocol provides a novel stereoselective synthesis of substituted cyclopentene and cyclopentane rings, as well as a new strategy for the efficient assembly of attached-ring structures. Further investigations on modifying and optimizing the Mo-cleavage reaction conditions to improve the stereoselectivity in the attached-ring system and the application of this method to the synthesis of natural products containing attached-ring structures are ongoing in our laboratory.

(30) Cleavage product **18f** was formed as a single stereoisomer (*cis*). However, upon standing at room temperature for 1 week, ^{1}H NMR indicated the *cis*-**18f** product was epimerized to a 60:40 mixture of *cis* and *trans* isomers.

Table 2. Mo-Mediated Cleavage Reactions of Intramolecular Cycloadducts **8a**−**e**



entry	cycloadduct	R	X	cleavage product	yield[a]
1	**8a**	H	CH_2	**24a**[b]	62%
2	**8b**	H	CH_2CH_2	**24b**[c]	60%
3	**8c**	H	O	**24c**[d]	53%



entry	cycloadduct	R	X	cleavage product	yield[a]
4	**8d**	Hexyl	CH_2	**24d**[b]	73%
5	**8e**	CH_2OMe	CH_2	**24e**[e]	67%

[a] Isolated yields after column chromatography. [b] As a 67:33 mixture of two stereoisomers (at C_3). [c] As a 60:40 mixture of two stereoisomers (at C_3). [d] As a 50:50 mixture of two stereoisomers (at C_3). [e] As a mixture of four stereoisomers (at C_1 and C_3)

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

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