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Molybdenum Oxides as Highly Effective Dehydrative Cyclization Catalysts for the Synthesis of Oxazolines and Thiazolines

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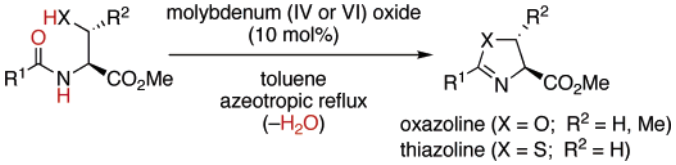
ABSTRACT

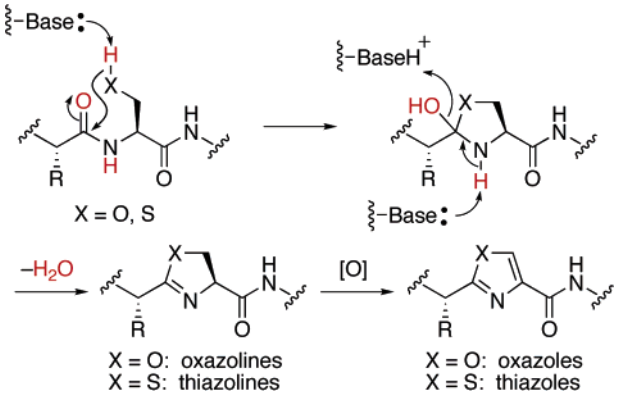


In the presence of molybdenum oxide the dehydrative cyclization of *N*-acylserines, *N*-acylthreonines, and *N*-acylcysteines can be carried out under Dean–Stark conditions in toluene to give oxazolines and thiazolines. The ammonium salts $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and $(NH_4)_2MoO_4$ have excellent catalytic activities for the dehydrative cyclization of serine and threonine derivatives, and the acetylacetonate complex $MoO_2(acac)_2$ has a remarkable catalytic activity for the dehydrative cyclization of cysteine derivatives. In addition, polyaniline-supported $MoO_2(acac)_2$ can easily be recovered and reused.

Oxazoline, oxazole, thiazoline, and thiazole rings are important constituents of numerous bioactive natural products and pharmaceuticals.[1] The biosynthesis of many naturally occurring oxazolines and thiazolines appears to involve the dehydrative cyclization of serine, threonine, and cysteine residues.[1c] Oxazoles and thiazoles are synthesized by the oxidation of oxazolines and thiazolines, respectively (Scheme 1).

Although several stoichiometric reagents are known to be effective for the dehydrative cyclization of *N*-(*β*-hydroxyethyl)amides or *N*-(*β*-mercaptoethyl)amides to oxazolines or thiazolines,[2] few successful examples of dehydrating catalysts have been reported: 3-nitrophenylboronic acid,[3] a lanthanide chloride,[4] a zeolite,[5] $TiCl_4$,[6] TsOH,[7] etc. In these catalytic reactions, the addition of an excess amount of substrate or heating to a high reaction temperature is required because of their low catalytic activities. In addition, these catalytic methods are limited to simple acid- or base-tolerant substrates that do not have any other functional groups. In this communication, we describe a biomimetic synthesis of oxazolines and thiazolines catalyzed by molybdenum (IV or VI) oxides.[8] To the best of our knowledge, this is the first

Scheme 1. Proposed Biosynthesis of Oxazolines, Thiazolines, Oxazoles, and Thiazoles



(1) (a) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 584 and references therein. (b) Lewis, J. R. *Nat. Prod. Rep.* **2002**, *19*, 223 and references therein. (c) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249.

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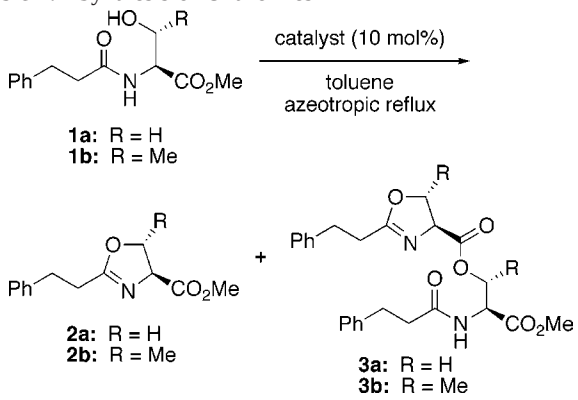
example of the catalytic dehydrative cyclization of dipeptide substrates that include serine, threonine, and cysteine residues.

In the course of screening various metal oxides as catalysts for the dehydrative cyclization of *N*-(3-phenylpropionyl)-L-serine methyl ester (**1a**) to oxazoline **2a**, we found that molybdenum oxides (MoO_2, MoO_3) had good catalytic activities (entries 1 and 2, Table 1). Hence, we investigated

Table 1. Synthesis of Oxazolines **2**[a]

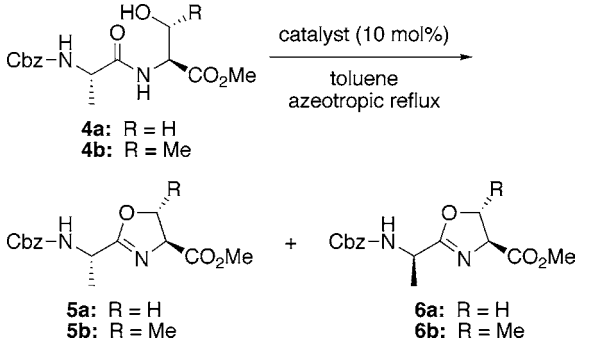


		1a → 2a		1b → 2b	
entry	catalyst	time (h)	yield (%)[b,c]	time (h)	yield (%)[b,c]
1	MoO_2	8	86 (10)	8	97 (0)
2	MoO_3	8	78 (5)	8	99 (0)
3	$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$	4	87 (11)	2	97 (0)
4	$(NH_4)_2MoO_4$	4	89 (11)	2	95 (0)
5	$MoO_2(acac)_2$	1	87 (7)	1	90 (0)
6	3-$(NO_2)C_6H_4B(OH)_2$	8	3 (0)	8	4 (0)
7	no catalyst	8	0 (0)	8	0 (0)

[a] Reactions were carried out with 0.5 mmol of substrate and 10 mol % of catalyst in toluene (50 mL for serine derivatives and 10 mL for threonine derivatives) at azeotropic reflux with the removal of water. [b] Determined by HPLC analysis. [c] Yield of **3a** or **3b** in parentheses.

the catalytic activities of several commercially available molybdenum oxides. In the presence of 10 mol % of molybdenum oxide, a solution of serine derivative **1a** and threonine derivative **1b** in toluene was heated at reflux with the azeotropic removal of water for several hours. After removal of the solvent, the resulting crude products were analyzed by HPLC. The ammonium salts and acetylacetonate complex of molybdenum(VI) oxide such as $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, $(NH_4)_2MoO_4$, and $MoO_2(acac)_2$, as well as MoO_2 and

Table 2. Synthesis of Oxazolines **5**[a]



		4a → 5a		4b → 5b	
entry	catalyst	time (h)	yield (%)[b,c]	time (h)	yield (%)[b,c]
1	MoO_2	8	80 (4)	2.5	80 (5)
2	MoO_3	8	83 (2)	3	82 (6)
3	$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$	2.5	90 (0)	2	86 (5)
4	$(NH_4)_2MoO_4$	1	93 (0)	1.5	84 (8)
5	$MoO_2(acac)_2$	1	68 (0)	1	82 (11)

[a] Reactions were carried out with 0.5 mmol of substrate and 10 mol % of catalyst in toluene (50 mL for serine derivatives and 10 mL for threonine derivatives) at azeotropic reflux with the removal of water. [b] Determined by HPLC analysis. [c] Yield of **6a** or **6b** in parentheses.

MoO_3, were also found to have good catalytic activities. 3-Nitrophenylboronic acid[3] showed lower catalytic activity than molybdenum oxides under the same conditions (entry 6). In the reaction of **1a**, a small amount of dimer **3** was obtained as a byproduct. The yield of dimer **3** could be reduced by conducting the reactions under high-dilution conditions (10 mM). When the reaction of **1a** was carried out using $(NH_4)_2MoO_4$ at a higher concentration (50 mM), **2a** was obtained in 53% yield along with **3** in 27% yield.

We then examined the dehydrative cyclization of more complex dipeptide substrates, Cbz-L-Ala-L-Ser-OCH_3 (**4a**) and Cbz-L-Ala-L-Thr-OCH_3 (**4b**). Surprisingly, the ammonium salts of molybdenum(VI) oxides, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and $(NH_4)_2MoO_4$, exhibited remarkable catalytic activities and gave oxazolines **5a** and **5b** in a short reaction time, along with small amounts of **6a** and **6b**, which are epimers at the α-position of the alanine residue (Table 2).[9]

Next, we examined the dehydrative cyclization of cysteine derivatives to thiazolines using molybdenum oxides as catalysts (Table 3). In the case of *N*-(3-phenylpropionyl)-L-cysteine methyl ester (**7a**), $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, $(NH_4)_2MoO_4$, and $MoO_2(acac)_2$ showed excellent catalytic

(2) (a) Martin's sulfrane: Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **2002**, *43*, 8679. (b) DAST: Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165. (c) Burgess reagent: Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907. (d) Mitsunobu reagent: Galéotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807. (e) Mitsunobu reagent: Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267. (f) Ph_2SO-Tf_2O: Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett* **1992**, 153. (g) DAST: Burrell, G.; Evans, J. M.; Jones, G. E.; Stemp, G. *Tetrahedron Lett.* **1990**, *31*, 3649. (h) PPh_3-CCl_4: Meyers, A. I.; Denton, H. *Tetrahedron Lett.* **1985**, *26*, 4687. (i) PPh_3-CCl_4: Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471. (j) Ph_3PO-Tf_2O: You, S.-L.; Razavi, H.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 83.

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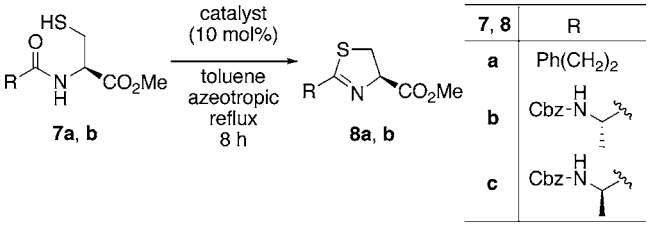
(6) (a) Raman, P.; Razavi, H.; Kelly, J. K. *Org. Lett.* **2000**, *2*, 3289. (b) Kuriyama, N.; Akaji, K.; Kiso, Y. *Tetrahedron* **1997**, *53*, 8323. (c) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5566.

(7) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230.

Table 3. Synthesis of Thiazolines **8**[a]

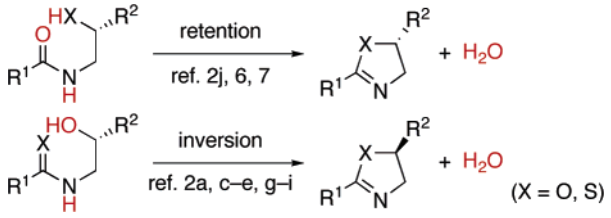


entry	catalyst	**7a** → **8a** yield (%)[b]	**7b** → **8b** yield (%)[b]
1	MoO_2	29[c]	6[c]
2	MoO_3	18[c]	9[c]
3	$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$	96[c]	16[c]
4	$(NH_4)_2MoO_4$	99[c]	26[c]
5	$MoO_2(acac)_2$	81 (98.7% ee)[d]	70 (15)[e,f]
6	no catalyst	9[c]	0[c]

[a] Reactions were carried out with 0.5 mmol of substrate and 10 mol % of catalyst in toluene (50 mL) at azeotropic reflux with the removal of water for 8 h. [b] Determined by ^{1}H NMR analysis. [c] Enantiomeric exess or diastereomeric ratio of the product was not determined. [d] Determined by HPLC analysis on Chiralcel OD-H. [e] 5 h. [f] Yield of **8c** in parentheses. Determined by HPLC analysis on Develosil 30−5.

activities, giving thiazoline **8a** (respective yields of 96%, 99%, and 81%, entries 3−5) without any byproducts, whereas MoO_2 and MoO_3 showed lower activities (entries 1 and 2). The optical purity of **8a** obtained by the reaction using $MoO_2(acac)_2$ was 98.7% ee. $MoO_2(acac)_2$ could catalyze the dehydrative cyclization of a more complex dipeptide substrate, Cbz-L-Ala-L-Cys-OCH_3 (**7b**), to give thiazoline **8b** in 70% yield along with diastereomer **8c** in 15% yield (entry 5).[10] Other molybdenum oxides exhibited poor catalytic activities in the dehydrative cyclization of **7b** (entries 1−4). The dehydrative cyclization of cysteine derivatives **7a** and **7b** was conducted under high-dilution conditions (10 mM of substrates). When the dehydrative cyclization reaction of **7b** was conducted at a higher substrate concentration (50 mM), lower yields of thiazolines **8b** (62%) were obtained.

(8) For the chemical synthesis of oxazolines/thiazolines, there are two methodoligies: one is the retentive cyclization of *N*-(*β*-hydroxyethyl)amides/*N*-(*β*-mercaptoethyl)amides (biomimetic synthesis) at the *β*-position, the other is its invertive cyclization.

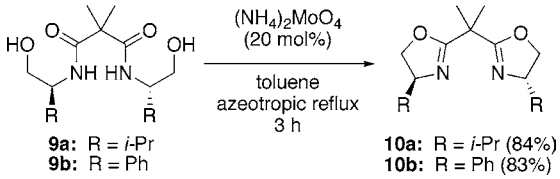


(9) Corey et al. reported the dehydrative cyclization of a threonine derivative using TsOH as a catalyst (ref 7). Dehydrative cyclization of **4b** using TsOH gave **5b** in 48% yield along with **6b** in 50% yield, probably due to its strong acidity.

(10) Kelly et al. reported that the deprotection-cyclodehydration of Cbz-L-Phe-L-Cys(Tr)-OCH_3 using $TiCl_4$ at 0 °C afforded a 1: 1 mixture of the corresponding diastereomeric thiazoline (60% yield, ref 6a). Although the dehydrative cyclization of **7b** using $MoO_2(acac)_2$ was conducted at high reaction temperature (toluene reflux), the loss of stereochemical integrity was less than with the reaction using $TiCl_4$, which was mainly because the molybdenum oxide is a nearly neutral compound.

Bis(oxazoline)s are a very useful class of chiral ligands for asymmetric catalysis[11] and are generally synthesized from the corresponding bis(amide)s via sulfonylation or chlorination of the two hydroxyl groups. The present method was applied to the synthesis of bis(oxazoline)s (Scheme 2). Bis-

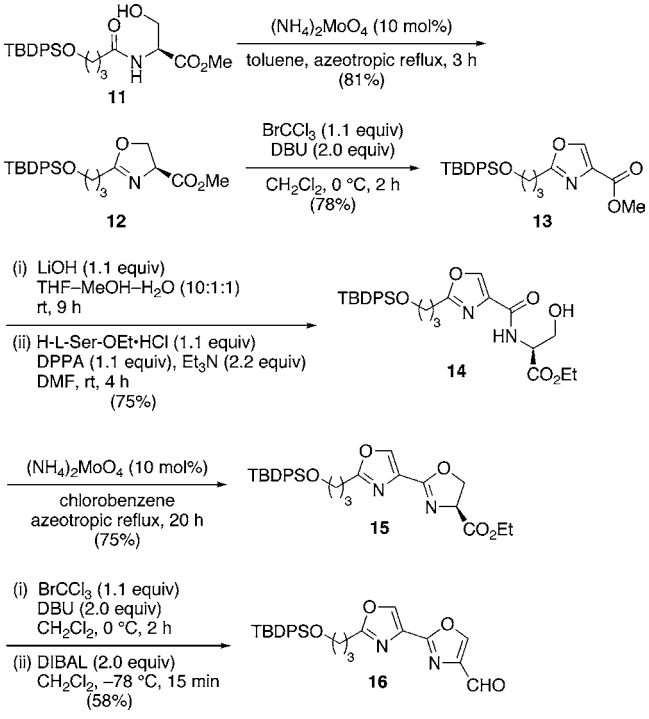
Scheme 2. Synthesis of Bis(oxazoline)s **10**, Chiral Ligands for Asymmetric Catalysis



(amide)s **9a** and **9b** were reacted with 20 mol % of $(NH_4)_2MoO_4$ at azeotropic reflux with the removal of water for 3 h. After purification by silica gel chromatography, bis(oxazoline)s **10a** and **10b** were obtained in respective yields of 84% and 83%.

We next tried to synthesize a key synthetic intermediate **16** of a natural bioactive compound, hennoxazole A[12] (Scheme 3). Dehydrative cyclization of serine derivative **11**

Scheme 3. Synthesis of **16**, a Key Intermediate of Hennoxazole A

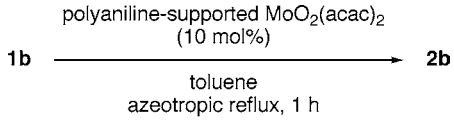


using 10 mol % of $(NH_4)_2MoO_4$ gave oxazoline **12** in 81% yield. The oxidation of oxazoline **12** to oxazole **13** by the

(11) (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.

reported procedure,[12] hydrolysis of the methyl ester of **13**, and subsequent amide condensation with L-serine ethyl ester gave **14** in 59% overall yield from **12**. Dehydrative cyclization of **14** using 10 mol % of $(NH_4)_2MoO_4$ in chlorobenzene gave oxazoline **15** (75%) along with recovered **14** (8%). Oxidation of the oxazoline ring[13] and reduction of the ethyl ester of **15** gave **16** in 58% yield.

Scheme 4. Dehydrative Cyclization Using Polyaniline-Supported $MoO_2(acac)_2$ as a Recyclable Catalyst



run	1	2	3	4	5
yield (%)	99	95	91	92	87

Next, we examined polymer-supported molybdenum oxides as recyclable catalysts. Polyaniline-supported $MoO_2(acac)_2$[14] also catalyzed efficiently the dehydrative cyclization of **1b**. The immobilized catalyst was recovered by filtration and reused more than five times for the dehydrative cyclization of **1b** (Scheme 4).

In conclusion, we have developed an efficient molybdenum oxide catalyzed dehydrative cyclization of serine, threonine, and cysteine derivatives, which gives oxazolines and thiazolines in good yield. In particular, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and $(NH_4)_2MoO_4$ showed excellent catalytic activities for the dehydrative cyclization of serine and threonine derivatives, and $MoO_2(acac)_2$ had a remarkable catalytic activity for the dehydrative cyclization of cysteine derivatives. The present method can be applied to a wide range of complex substrates because the reaction proceeds under neutral conditions. Mechanistic studies and the application of this method to the synthesis of more complex natural products are in progress.

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

OL050543J

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(14) Velusamy, S.; Ahamed, M.; Punniyamurthy, T. *Org. Lett.* **2004**, *6*, 4821.