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Efficient Syntheses and Ring-Opening Reactions of *trans*- and *cis*-Oxazoline-5-carboxylates

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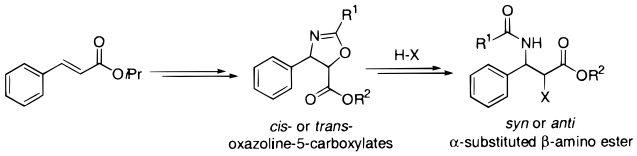
ABSTRACT



***cis*- and *trans*-Oxazoline-5-carboxylates were synthesized efficiently from isopropyl *trans*-cinnamate utilizing the Sharpless AA reaction. *trans*-Oxazoline was much more reactive than the *cis*-isomer toward ring opening reactions. From ab initio molecular calculations, the *cis*-isomer was predicted to be less reactive than the *trans*-isomer by 2.7 kcal/mol. Both *syn* and *anti* acetylthio esters and *anti* diamino esters were synthesized from these *cis*- and *trans*-oxazoline-5-carboxylates.**

Oxazolines are present in many biologically active natural products,[1] and chiral oxazolines are also widely applied as powerful tools in asymmetric synthesis.[2] Among them, the enantioselective synthesis of oxazoline-4-carboxylates and their ring-opening reactions are relatively well studied.[3] Noteworthy was a paper reported by Laaziri[4] and co-workers, in which serine or threonine was exploited as a starting material for the synthesis of oxazoline-4-carboxylate. The ring opening of these oxazolines with a chloroformate or a trimethylsilyl halide was used to prepare *N*,(*N*)-protected β-halogeno α-amino esters. As Laaziri mentioned in his paper, oxazoline-4-carboxylate can be considered as the synthetic equivalent of a β-cation (Figure 1). Aziridine-2-carboxylate is also known to be the synthetic equivalent of either a β- or α-cation when R^1 is an aliphatic substituent.

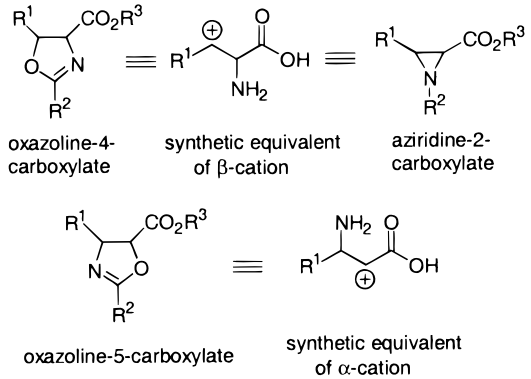


Figure 1. Oxazoline-4-carboxylate and aziridine-2-carboxylate as the synthetic equivalent of a β-cation; oxazoline-5-carboxylate as the synthetic equivalent of an α-cation.

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(1) For recent leading references, see: (a) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771. (b) Michael, J. P.; Pattenden, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1 and refs therein.
(2) (a) Frump, J. A. *Chem. Rev.* **1971**, *71*, 483. (b) Gant, T. G.; Meyers A. I. *Tetrahedron* **1994**, *50*, 2297 and refs therein.
(3) (a) Wipf, P.; Miller, C. P.; Venkatraman, S.; Fritch, P. C. *Tetrahedron Lett.* **1995**, *36*, 6395. (b) Wipf, P.; Venkatraman, S. *Synlett* **1997**, 1 and refs therein. (c) Suga, H.; Ikai, K.; Ibata, T. *Tetrahedron Lett.* **1998**, *39*, 869.
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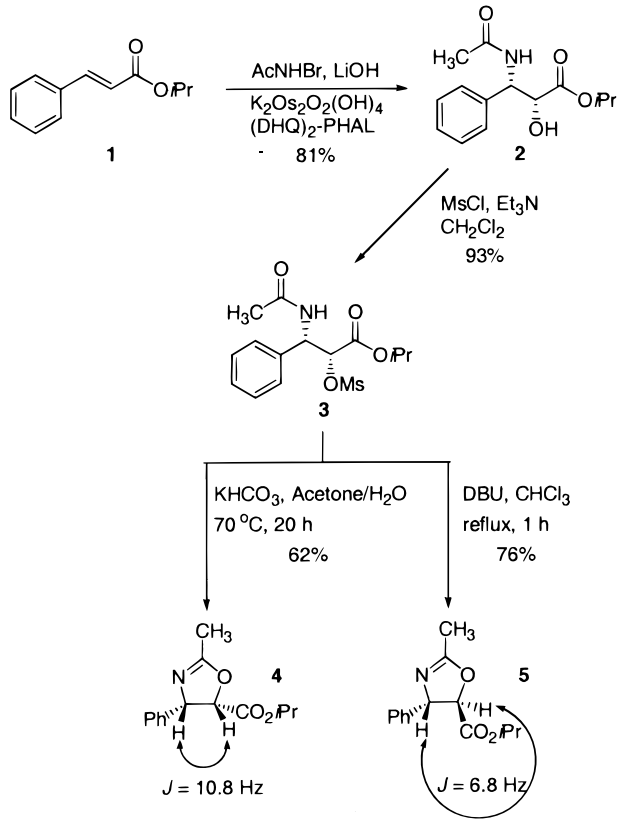
In particular, when R^1 is an aromatic substituent, a ring-opening reaction occurs, mainly at the 3-position (benzylic position) of the aziridine ring.[5] On the other hand, oxazoline-5-carboxylate can be a useful intermediate as the synthetic equivalent of an α-cation for the preparation of α-substituted *β*-amino esters. Unlike oxazoline-4-carboxylate, we found that oxazoline-5-carboxylates were utilized by many groups,[6] but mainly as an intermediate for *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine, a taxol C-13 side chain. Herein, we report an efficient synthesis of both *cis*- and *trans*-oxazoline-5-carboxylates as well as their ring-opening reactions.

Commercially available isopropyl *trans*-cinnamate (**1**) was the starting point of our synthesis (Scheme 1). Amino alcohol

Scheme 1



2 was obtained in 81% yield following the reported Sharpless AA reaction.[7] Amino alcohol **2** was then converted to its methanesulfonate **3**, which was successfully transformed to *cis*-oxazoline **4** with a clean inversion of configuration at the α-center in 62% yield with potassium bicarbonate in acetone−water. On the other hand, treatment of methanesulfonate **3** with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in refluxing chloroform for 1 h gave *trans*-oxazoline **5** with net retention of configuration in 76% yield with a trace of *cis*-oxazoline **4**, which can be removed by column chromatography. Epimerizations of *cis*-oxazoline-4-carboxylate or *cis*-imidazoline to its thermodynamically more stable *trans*-isomer using triethylamine were reported very recently.[8,3c] However, in our case, we did not observe any epimerization from *cis*-oxazoline to *trans*-oxazoline in refluxing chloroform in the presence of DBU. We believe epimerization of **3** to anti methanesulfonate occurred first, then *trans*-oxazoline was obtained from this intermediate. The NMR spectra of the *cis*-isomer **4** and the *trans*-isomer **5** showed a distinct difference in the coupling constants. The coupling constant between H-4 and H-5 for the *cis*-isomer **4** was 10.8 Hz and that for the *trans*-isomer **5** was 6.8 Hz.

Ring-opening reactions of *trans*- and *cis*-oxazoline-5-carboxylates are summarized in Table 1. When trimethylsilyl azide was used as an azide source for the synthesis of the α,*β*-diamino acid derivative, we found that there were huge differences in reactivity between the *trans*- and *cis*-oxazoline compounds. Treatment of *trans*-oxazoline **5** with trimethylsilyl azide in methanol at 70−80 °C led to the *trans*-azide **6** in 90% yield. However, even at higher reaction temperature or in the presence of additional Lewis acid such as boron trifluoride diethyl etherate ($Et_2O{\cdot}BF_3$) or trimethylsilyl triflate (TMSOTf), only unreacted *cis*-oxazoline **4** was recovered in an attempt to open this oxazoline ring with trimethylsilyl

Table 1. Ring-Opening Reaction of *trans*- and *cis*-Oxazoline-5-carboxylates (**5**, **4**)

Substrate / Reaction Condition	**5**	**4**
HN_3 (TMS-N_3 /MeOH), 70-80 °C, 2-3 days	**6** (yield; 90%)	No reaction even at higher reaction temp.(90 °C) in the presence of additional Lewis acid such as BF_3OEt_2 or TMSOTf
C_6H_5SH, MeOH, 70 °C, 2 days	**7** (yield; 96%)	No reaction
CH_3COSH THF, 70 °C, 12 h	**8** (yield; 78%)	**9** (yield; 53%)

(5) (a) Papa, C.; Tomasini, C. *Org. Lett.* **1999**, *1*, 2153. (b) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.

(6) (a) Gou, D.-M.; Liu, Y.-C.; Chen, C.-S. *J. Org. Chem.* **1993**, *58*, 1287. (b) Kingston, D. G. I.; Chaudhary, A. G.; Gunatilaka, A. A. L.; Middleton, M. L. *Tetrahedron Lett.* **1994**, *35*, 4483. (c) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1375. (d) Chen, S.-H.; Farina, V.; Vyas, D. M.; Doyle, T. W.; Long, B. H.; Fairchild, C. *J. Org. Chem.* **1996**, *61*, 2065.

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azide. To explain the poor reactivity of *cis*-oxazoline, we carried out ab initio molecular orbital calculations (Figure 2).[9] The *cis*-oxazoline **4-Me**[10] was found to be less stable

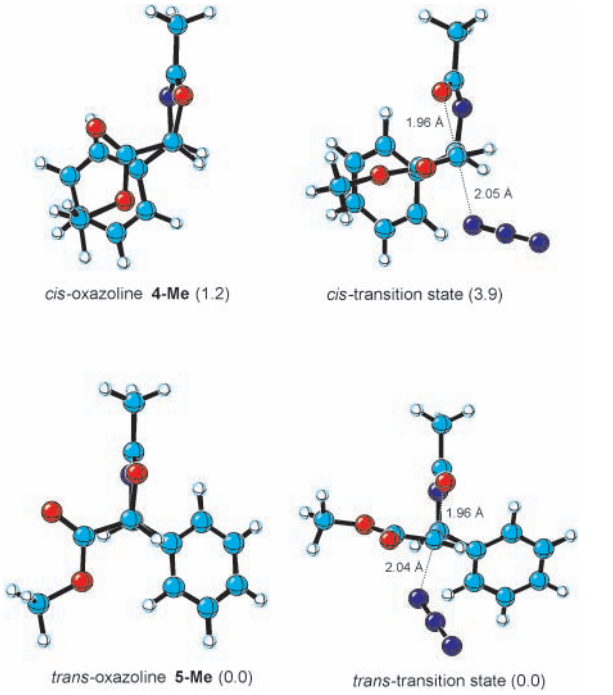
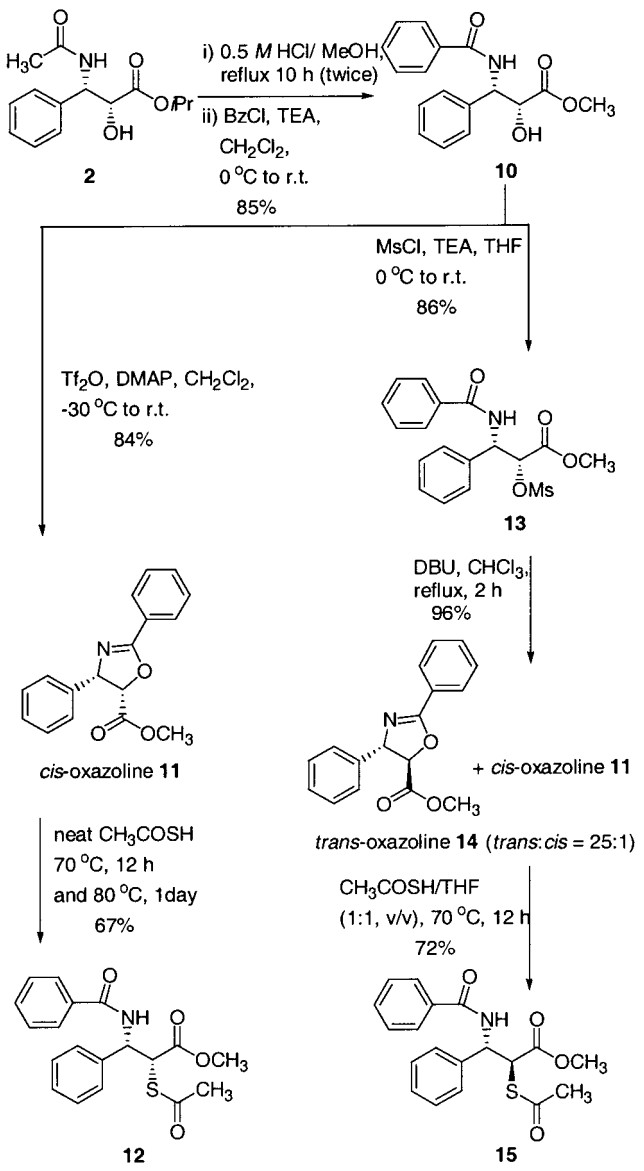


Figure 2. Ab initio molecular orbital calculations.

than the *trans*-oxazoline **5-Me** by 1.2 kcal/mol at the RHF/6-31G* level. This is due to the steric repulsion between the phenyl and ester groups in close contact. However, the relative instability of the reactant does not explain the lower reactivity of the *cis*-isomer. At the transition state for ring opening upon azide attack, the *cis*-isomer is found to be less stable by 3.9 kcal/mol at the same level of theory. Therefore, the *cis*-oxazoline is less reactive than the *trans*-oxazoline by 2.7 kcal/mol. The difference in activation energy is worth more than 100-fold difference in the reaction rate at room temperature. The reason that the energy difference between the *cis*- and *trans*-isomers is larger in the transition state than in the ground state can be seen from the structures. At the transition state, the ester group is in a perpendicular orientation to the forming and breaking bonds, to maximize the resonance between the p-orbitals of the carbonyl and the reaction center carbons. This makes steric repulsion between the phenyl and ester groups in the *cis*-orientation more severe.

We observed similar results when thiophenol was used as a reagent. Phenylthioether **7** was obtained in 96% yield,

Scheme 2



whereas *cis*-oxazoline was unreactive under the same conditions. However, when thiolacetic acid was used, both the *anti* and *syn* acetylthio esters (**8**, **9**) were isolated in 78% and 53% yields, respectively. This result may be due to the better reactivity of thiolacetic acid toward the ring opening reactions than the other reagents. Either amino alcohol **2** or methanesulfonate **3** can be considered as candidates for the synthetic equivalent of an α-cation. However, we could not obtain the desired acetylthio ester from **2** using the Mitsunobu reaction conditions (DEAD, PPh_3, thiolacetic acid). An attempt to displace the methanesulfonate group in **3** by the acetylthio group using triethylamine and thiolacetic acid also failed.

To show the possible utility of these oxazoline-5-carboxylates, 2′-sulfur analogues and nitrogen analogues of the taxol C-13 side chain were prepared. To change the *N*-protecting group from an acetyl group to a benzoyl group, amino alcohol **2** was refluxed in 0.5 M methanolic HCl for 10 h

(9) Gaussian 94, Revision B.3, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Pittsburgh, PA, 1995.

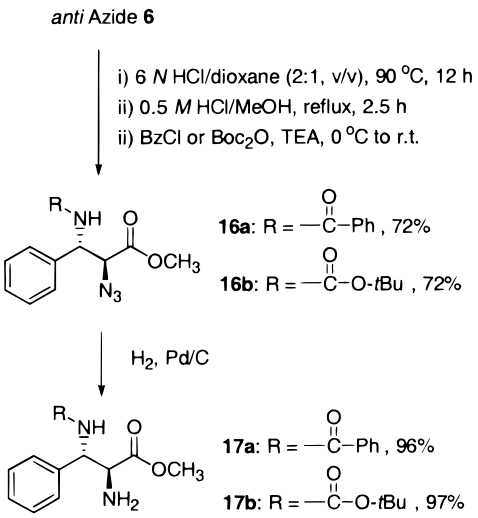
(10) For computational simplification, the isopropyl group of **4** and **5** was replaced with a methyl group to provide **4-Me** and **5-Me**, respectively.

(twice) followed by benzoyl protection using benzoyl chloride (BzCl) and triethylamine (Scheme 2). In this step, transesterification of the isopropyl ester to the methyl ester also occurred. Treatment of **10** with triflic anhydride (Tf_2O) afforded *cis*-oxazoline **11** in 84% yield.[11] When this *cis*-oxazoline **11** was reacted with neat thiolacetic acid, *syn* acetylthio ester **12** (2*R*,3*S*) was obtained in 67% yield after heating for 12 h at 70 °C and additional heating for 1 day at 80 °C. This reaction needed a much longer reaction time because *cis*-oxazoline is much less reactive toward the ring opening reaction than is *trans*-oxazoline. On the other hand, treatment of methanesulfonate **13** with DBU afforded both *trans*- and *cis*-oxazolines (**14**, **11**) in a ratio of 25 to 1. Unlike 2-methyl oxazoline, we failed to isolate 2-phenyl *trans*-oxazoline by column chromatography. However, from this mixture, we could obtain the diastereomerically pure *anti* acetylthio ester **15** (2*S*,3*S*) in 72% yield under rather mild conditions (70 °C, 12 h) with thiolacetic acid/tetrahydrofuran (1:1) after chromatography.

The selectively protected *anti* isomer of methyl 2-amino-3-(benzoylamino)-3-phenylpropionate (**17a**) and methyl 2-amino-3-(*tert*-butoxycarbonylamino)-3-phenylpropionate (**17b**) were synthesized from azide **6** (Scheme 3). After sequential hydrolysis, esterification, and appropriate *N*-protection, either the benzoyl or the Boc-protected *anti* azide methyl ester (**16a, 16b**) were obtained. Catalytic hydrogenation of the azide group gave the *anti* diamino esters **17a** (>98% de) and **17b** (>97% de) in 69% and 70% yields, respectively. Less than 2% epimers were detected in both products by ^{1}H NMR. They were probably produced during the heating (90 °C) in acidic solution.

In conclusion, we have shown an efficient stereoselective synthesis of *cis*- and *trans*-oxazoline-5-carboxylates and their ring-opening reactions. In addition, we have shown that oxazoline-5-carboxylate can be a powerful intermediate as a synthetic equivalent of an α-cation for the preparation of α-substituted β-amino esters.

Scheme 3



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Supporting Information Available: Experimental procedures and characterization data for the compounds described in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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