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Efficient cyclization of ω-oxo-α,β-unsaturated esters using lithium thiolate-initiated Michael-aldol tandem reaction

Masashi Ono, Katsumi Nishimura, Yasuo Nagaoka and Kiyoshi Tomioka *

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

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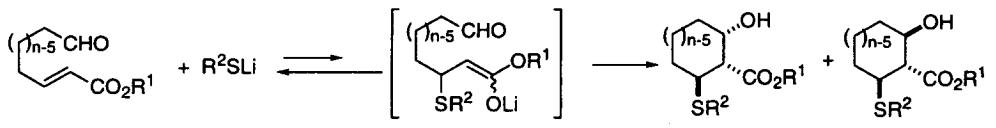
Abstract

The reaction of ω-oxo-α,β-unsaturated esters with lithium thiolates afforded the Michael-aldol tandem cyclization products in good to perfect stereoselectivity depending on the nature of thiolates.

A carbon–carbon bond forming methodology for cyclization is of importance in the synthetic chemistry of carbocycles.[1] Since the reaction of a lithium ester enolate with an aldehyde is the most powerful and convenient process for a carbon–carbon bond formation, it is highly desirable to establish a methodology for selectively generating lithium enolate of an ester bearing an enolizable aldehyde in the same molecule. Such possibility is reasonably designed if the lithium ester enolate is generated through the Michael reaction of a lithiated nucleophile with an enoate bearing a ω-formyl group. We have recently reported the lithium benzenethiolate-initiated Michael addition-intermolecular aldol tandem reaction of enoates with aldehydes.[2] The reaction is characterized by the coexistence of an enoate and an aldehyde when a catalytic nucleophile, lithium benzenethiolate, is loaded. We describe herein that extension of the process into the reaction of ω-oxo-α,β-unsaturated esters **1** with benzenethiolate **2** (R^2=Ph) provided the expected cyclization product **4** via ω-formylenolate **3** in a good *cis* stereoselectivity (Scheme 1).[3,4] Furthermore, the cyclization using lithium benzylthiolate **2** (R^2=$PhCH_2$) gave *cis*-**4** in a perfect stereoselectivity and high yield.[5]



1 **2** **3** ***cis*-4** ***trans*-4**

Scheme 1. The Michael-aldol tandem cyclization

* Corresponding author.

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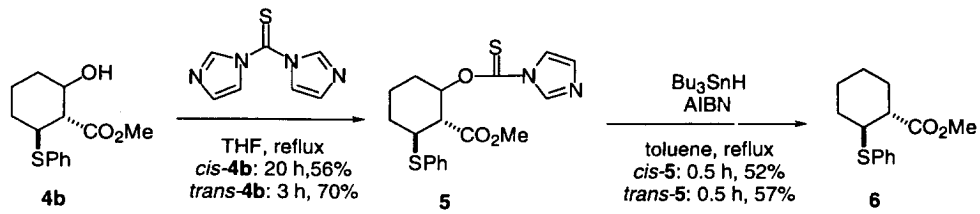
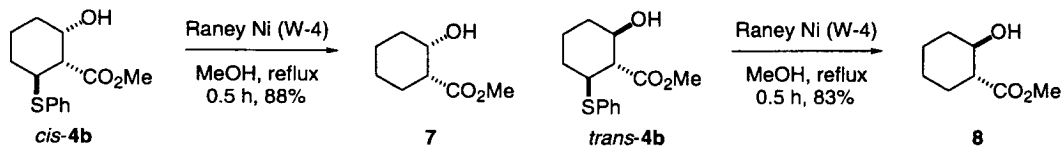
Table 1
Michael-aldol tandem cyclization of **1** giving **4** initiated by lithium thiolate **2**

Entry	**1**	n	R^1	R^2	Eq	Additive	Eq	Temp/°C	Time/h	cis-**4**/%	trans-**4**/%
1	**a**	5	Et	PhS	0.2	PhSTMS	2.0	0	2	37	0
2	**a**	5	Et	$PhCH_2S$	1.2	none		0	0.5	96	0
3	**b**	6	Me	PhS	0.2	PhSTMS	2.0	0	2	61	18
4	**b**	6	Me	PhS	1.2	none		–20	1	24	5
5	**b**	6	Me	PhS	1.2	$AlMe_3$	1.2	0	1	56	15
6	**b**	6	Me	$PhCH_2S$	1.2	none		–20	0.5	95	0
7	**c**	7	Et	PhS	0.2	PhSTMS	2.0	0	6	1	0
8	**c**	7	Et	$PhCH_2S$	1.2	$AlMe_3$	1.2	0	2	26	0
9	**c**	7	Et	$PhCH_2S$	1.2	none		0	0.5	33	0

Treatment of **1b**[6] (n=6, R^1=Me) with 0.2 equiv. of lithium benzenethiolate **2** (R^2=Ph) and 2 equiv. of phenyl trimethylsilyl (TMS) sulfide in THF at 0°C for 2 h gave **4b** (n=6, R^1=Me, R^2=Ph) as a mixture of two separable diastereomers in 61% and 18% yields (Table 1, entry 3).[7,8] Reductive removal of the hydroxy group of each diastereomers **4b** via **5** gave the identical *trans*-phenylsulfanylester **6**,[9] indicating that the two diastereomers of **4b** have the same relative stereochemistry at the carbons attaching the phenylsulfanyl and methoxycarbonyl groups (Scheme 2). On the other hand, Raney-nickel reduction of each diastereomer of **4b**, in turn, gave *cis*-hydroxyester **7** and *trans*-**8**, respectively (Scheme 3). The structures of **7** and **8** were readily assigned by NMR[10] and confirmed by the comparison of spectroscopic data with those reported.[11] These indicate that the two diastereomers of **4b** are each diastereomeric at the carbon bearing the hydroxy group and the major product is *cis*-**4b**.[12]

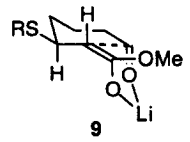


Scheme 2. Formation of **6** from *cis*- and *trans*-**4b**



Scheme 3. Formation of **7** and **8** from *cis*- and *trans*-**4b**

Formation of *cis*-**4b** as a major diastereomer is rationalized by the model shown in **9** (Fig. 1). The Michael addition of lithium benzenethiolate with enoate **1b** generates *cis*-enolate **3b**[13] of which lithium is coordinated by the formyl oxygen, and the phenylsulfanyl group (**9**: R=Ph) is *anti* to the coming formyl group, giving *cis*-**4b** as a TMS ether.[14] It is also important to point out that the enolate has the most stable allylic conformation as shown in **9**.[15] The contiguous three stereogenic centers of **4** are possible to be selectively constructed under these controls shown in **9**.



9

Figure 1. The model **9**

Since the overall reaction is thermodynamically in the equilibrium favoring starting lithium thiolate,[16] trap of the resulting lithium alkoxide of **4b** with phenyl TMS sulfide into a TMS ether of **4** is essential for the high stereoselectivity and high yield. In fact, the reaction of **1b** with 1.2 equiv. of lithium benzenethiolate **2** (R^2=Ph) in the absence of phenyl TMS sulfide at −20°C for 1 h gave *cis*- and *trans*-**4b** in 24% and 5% yields (Table 1, entry 4). Therefore, it is reasonable to observe that the reaction of **1b** with a more nucleophilic reagent, phenylthiotrimethylaluminium lithium,[3] at 0°C for 3 h and at rt for another 1 h gave *cis*- and *trans*-**4b** in 56% and 17% yields (entry 5).

Based on these results and consideration, we used lithium benzylthiolate as a more nucleophilic reagent, which is expected to give high stereoselectivity and high yield. Expectedly, the reaction of **1b** with 1.2 equiv. of lithium benzylthiolate **2** (R^2=$PhCH_2$) proceeded at −20°C for 0.5 h to afford stereoselectively *cis*-**4bb** (*n*=6, R^1=Me, R^2=$PhCH_2$) as an only isolable product in 95% yield (entry 6).[17] It is reasonably understandable that the reaction proceeded under kinetic control to give *cis*-**4bb** via **9**.

In addition to the cyclization of ω-oxo-α,β-unsaturated ester **1b** to six-membered carbocycles **4b** and **4bb**, those to five- and seven-membered ones **4a** and **4c** also proceeded with high stereoselectivity.

Cyclization of **1a** (*n*=5, R^1=Et) with **2** (R^2=Ph) in the presence of phenyl TMS sulfide at 0°C for 2 h gave selectively five-membered *cis*-**4a** (*n*=5, R^1=Et, R^2=Ph) as the only isolable product in 37% yield (entry 1). Cyclization of **1a** with benzylthiolate **2** (R^2=$PhCH_2$) was dramatically improved to afford, at 0°C for 0.5 h, *cis*-**4aa** (*n*=5, R^1=Et, R^2=$PhCH_2$) as the only product in 96% yield (entry 2). Cyclization of **1c** (*n*=7, R^1=Et) with benzylthiolate **2** (R^2=$PhCH_2$) at 0°C for 0.5 h gave selectively seven-membered *cis*-**4c** (*n*=7, R^1=Et, R^2=$PhCH_2$) in 33% yield (entries 7–9).[18]

In conclusion, the Michael-aldol tandem cyclization of ω-oxo-α,β-unsaturated esters with lithium benzylthiolate is a highly efficient methodology for the construction of five- to seven-membered carbocycles. Application to an asymmetric reaction and synthesis of biologically important compounds are the current interests of our research.

Acknowledgements

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6. The ω-oxo-α,β-unsaturated esters **1** were prepared by the Wittig reaction of the corresponding dialdehyde equivalents.
7. The ratio of *cis* to *trans* of these isomers of **4** was alternatively determined by NMR of the crude product. Other possible two isomers were not detected.
8. The new compounds described herein gave satisfactory analytical and spectroscopic data.
9. Reaction of methyl cyclohexenecarboxylate with lithium benzenethiolate gave stereoselectively *cis*-phenylsulfanylester, *cis*-form of **6**. Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974–12975.
10. The coupling constants between each methine protons, J=3.8 Hz for *cis*-**7** and J=9.9 Hz for *trans*-**8**, apparently supported the assignment.
11. Raney-nickel reduction of **4aa**,**b**,**bb**,**c** (n=5–7, R^2=Ph, $PhCH_2$) gave the corresponding hydroxyesters. Five-membered *cis*-hydroxyester: Seebach, D.; Roggo, S.; Maetzke, T.; Braunschweiger, H.; Cercus, J.; Krieger, M. *Helv. Chim. Acta* **1987**, *70*, 1605–1615. Six-membered *cis*-hydroxyester: Lubineau, A.; Queneau, Y. *J. Org. Chem.* **1987**, *52*, 1001–1007. Six-membered *trans*-hydroxyester: Narasaka, K.; Yamamoto, I. *Tetrahedron* **1992**, *48*, 5743–5754. Seven-membered *cis*-hydroxyester: Danchet, S.; Bigot, C.; Buisson, D.; Azerad, R. *Tetrahedron: Asymmetry* **1997**, *8*, 1735–1739.
12. The *cis*/*trans* refers the relationship between the carbons bearing the hydroxy and alkoxycarbonyl groups.
13. The *cis*-enolate refers the *syn* orientation of OLi and side chain. Formation of the *cis*-enolate is tentatively assigned based on the model **9**.
14. Protonation has been proposed to take place from a similar conformation. Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T.; Date, T.; Okamura, K.; Inagaki, S. *J. Org. Chem.* **1991**, *56*, 6556–6564.
15. (a) Tomioka, K.; Kawasaki, H.; Yasuda, K.; Koga, K. *J. Am. Chem. Soc.* **1988**, *110*, 3597–3601. (b) Kim, D.; Kim, H. S. *J. Org. Chem.* **1987**, *52*, 4633–4634.
16. The high acidity of benzenethiol is the origin of the equilibrium favoring starting materials.
17. The stereochemistry of *cis*-**4bb** (n=6, R^1=Me, R^2=$PhCH_2$) was assigned by analogy based on NMR.
18. General procedure (Table 1, entry 6): A solution of **1b** (156 mg, 1.0 mmol) in THF (2 mL) was added to a preformed solution of **2** (R^2=$PhCH_2$, 1.2 mmol), generated from benzylthiol (0.14 mL, 1.2 mmol) and butyllithium (0.75 mL, 1.2 mmol, hexane solution) at –20°C in THF (23 mL). The mixture was stirred for 0.5 h at –20°C. The resulting mixture was quenched with sat. NH_4Cl (20 mL), and extracted with AcOEt (30 mL). The combined organic extracts were washed with brine, and dried over Na_2SO_4. Concentration and purification by silica gel column chromatography (hexane/AcOEt=4/1) gave *cis*-**4bb** (266 mg, 95%) as a white solid of mp 52–53°C.