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The Conjugate Addition-Aldol Tandem Reaction of α,β-Unsaturated Esters Catalyzed By Lithium Benzenethiolate

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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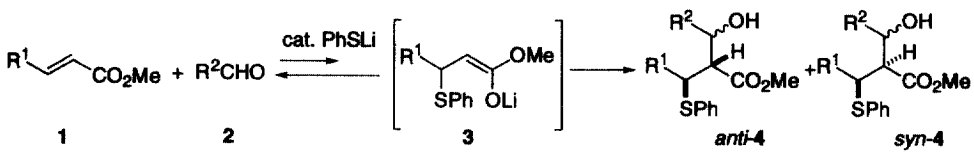
Abstract: Reactions of α,β-unsaturated esters with aldehydes were catalyzed by 0.2 equiv of lithium benzenethiolate in the presence of phenyl trimethylsilyl sulfide to afford the conjugate addition-aldol tandem reaction products in the *anti* stereoselectivity and good to high yields.

A catalytic methodology for a carbon-carbon bond formation is of prime importance in the synthetic organic chemistry.[1] The aldol-type reaction is an impressive recent advance, which utilizes a silyl enol ether and an aldehyde in the presence of a catalytic amount of promoters such as Lewis acid,[2] quaternary ammonium fluoride,[3] and metallic complex.[4] Another approach is the use of a transient enolate as a nucleophile, generated by the conjugate addition of a catalytic amount of a tertiary amine, a sulfide, and a phosphine to an α,β-unsaturated carbonyl compound, the so-called Baylis-Hillman reaction.[5] The generation of a metal enolate through the conjugate addition of tin[6] and aluminium[7] thiolates to an enone and subsequent trap with an aldehyde have been reported to afford the corresponding addition-electrophile trapping product.[8] Although the conjugate addition-aldol tandem reaction of a stoichiometric amount of magnesium thiolate with an enoate has been developed, the reaction with a stoichiometric amount of lithium thiolate lacks generality.[9,10] The merit of these reactions is the construction of three contiguous stereocenters, however, the stereochemical outcome has not yet been reported.[11]



Scheme 1. The conjugate addition-aldol tandem reaction.

We have been involved in the catalytic asymmetric conjugate addition reaction of lithium arylthiolates to the enoates, giving 3-arylsulfanylalkanoates.[12] The reaction proceeds through the generation and subsequent protonation of a transient lithium enolate. Our idea for the carbon-carbon bond formation relies on the use of the transient lithium enolate **3** thus generated. We describe herein that the reaction of an enoate **1** with an aldehyde **2** is catalyzed by lithium benzenethiolate in the presence of phenyl trimethylsilyl sulfide to afford stereoselectively, after protodesilylation, the corresponding addition-aldol tandem product **4** in

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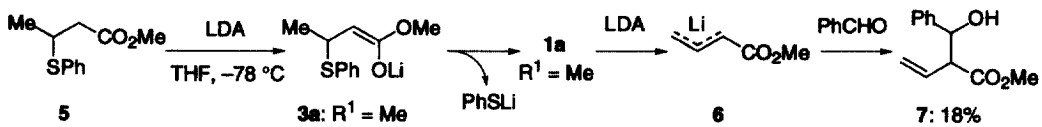
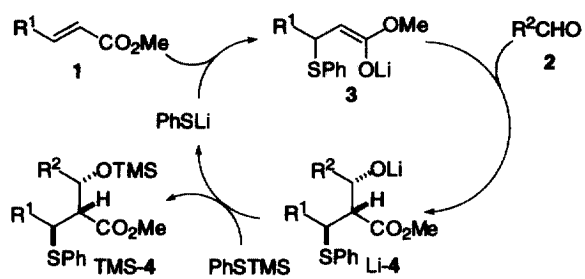
reasonably high yield (Scheme 1).

We began our studies with the generation of the lithium enolate **3a** (R^1 = Me). Treatment of **5** with LDA in THF at –78 °C for 0.5 h and then with benzaldehyde (**2**: R^2 = Ph), however, gave **7** in 18% yield without formation of the expected **4a** (R^1 = Me, R^2 = Ph). The ready retro-Michael reaction of **3a** produced back methyl crotonate **1a** (R^1 = Me) which was then deprotonated with LDA to result in an allylic anion **6** and then **7** as shown in Scheme 2. The lithium enolate **3a** is not stable enough to survive for the reaction with benzaldehyde.



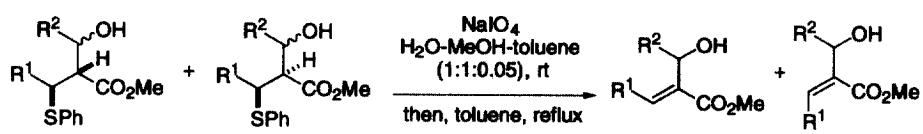
Scheme 2. Formation of **7**.

As the second trial, we attempted *in situ* trap of **3a**, generated by the conjugate addition of 1.2 equiv of lithium benzenethiolate to **1a**, with benzaldehyde in THF at rt to yield the expected product **4a** (R^1 = Me, R^2 = Ph) in 52% yield. It is reasonable to assume that the conversion of the lithium alkoxide moiety of the intermediate Li-**4a** into TMS-**4a** with phenyl trimethylsilyl sulfide should shift equilibrium to the target and simultaneously regenerate lithium benzenethiolate to achieve the catalytic cycle as shown in Scheme 3. Thus, treatment of **1a** with 0.2 equiv of lithium benzenethiolate in the presence of each 2 equiv of benzaldehyde and phenyl trimethylsilyl sulfide in THF at rt for 2 h provided, after protodesilylation with dilute aq. HCl, the expected product **4a** in 98% yield.[13]



Scheme 3. The catalytic process.

The *anti*/*syn* selectivity was determined by the treatment of **4** with sodium periodate and then thermal *syn*-elimination to afford the olefins **8**.[14] Thus, **4a**, a mixture of four stereoisomers in a ratio of 42 : 32 : 16 : 10, was converted to a mixture of *E*- and *Z*-olefins **8a** (R^1 = Me, R^2 = Ph) in a ratio of 74 : 26, corresponding to the ratio of *anti*- and *syn*-**4a** (Scheme 4).[15]



Scheme 4. Formation of *E*- and *Z*-**8** from *anti*- and *syn*-**4**.

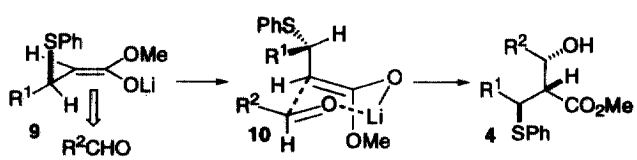
The stereoselectivity of *anti*- to *syn*-**4a** was improved to 89 : 11 by changing the reaction solvent to toluene from THF as shown in Table 1, entry 1.[16]

Table 1. Reaction of **1** with **2** Catalyzed by Lithium Benzenethiolate Producing **4** and Conversion to **8** [a]

				4[b]		**8**	
entry	R^1	R^2	time/h	yield/%	*anti* : *syn* [c]	yield/%	*E* : *Z* [d]
1	Me	Ph	2	92	89 (69:20) : 11 (8:3)	90	86 : 14
2	Me	4-MeOPh	3	90	80 (66:14) : 20 (14:6)	88	84 : 16
3	Me	4-ClPh	3	97	89 (68:21) : 11 (11:0)	95	89 : 11
4	Me	2-Py	3	56	83 (56:26) : 17 (9:8)	84	89 : 11
5	Me	2-Furyl	3	91	93 (60:33) : 7 (6:1)	47	>99 : 1
6	Me	*t*-Bu	16	83 [e]	>99 (>99:1) : 1	51	>99 : 1
7	Me	cHex	3	56 [e]	>99 (>99:1) : 1	88	>99 : 1
8	Bu	Ph	3	87	91 (69:22) : 9 (7:2)	70	93 : 7
9	Bu [f]	Ph	3	79	89 (73:16) : 11 (8:3)	80	83 : 14
10	Bn	Ph	3	88	82 (62:20) : 18 (13:5)		
11	Bn [f]	Ph	3	83	82 (65:17) : 18 (14:4)		
12	Ph	Ph	5	81	94 (83:11) : 6 (3:3)		

a) The reaction was carried out in toluene at rt. b) The ester **5** was formed in the yield of 34% (entry 4) and 43% (entry 7). c) The ratio of *anti*- to *syn*-**4** was determined by NMR. d) The ratio of *E*- to *Z*-**8** was determined by NMR. e) A single isomer **4** was obtained (Scheme 5). f) *Z*-olefin was used.

Six enoates **1** (R^1 = Me, Bu (*E*- and *Z*-), Bn (*E*- and *Z*-), Ph) were converted to **4** in *anti* stereoselectivity and high yields (Table 1).[17] The most major isomer is the same as **4** shown in Scheme 5. Reactions of **1a** (R^1 = Me) with pivalaldehyde and cyclohexanecarbaldehyde provided **4** (R^1 = Me, R^2 = *t*-Bu, c-Hex) as a single isomer having contiguous three stereocenters (entry 6, 7). The model **10** is responsible for the establishment of the stereochemistry of the three contiguous stereogenic centers in **4** (R^1 = Me, R^2 = *t*-Bu, c-Hex; Scheme 5).



Scheme 5. Diastereoselective aldol reaction.

Regardless of whether *E*- or *Z*-olefin **1** (R^1 = Bu, Bn) was used, almost identical stereoselection was observed in the formation of **4** (entry 8, 9, and 10, 11). These findings indicate that aldol reaction of the transient lithium enolate **3** with aldehyde **2** takes place from the bottom face attack, *anti* to the phenylsulfanyl group in the thermodynamic enolate conformation **9** (Scheme 5). These selectivities in the carboelectrophile trap are different from the protonation in which the protonation takes place from the kinetic enolate.[18]

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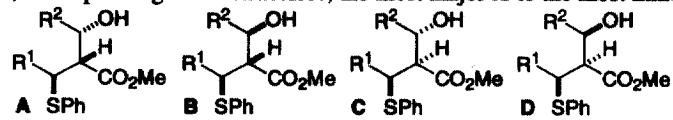
(13) The new compounds described herein gave satisfactory analytical and spectroscopic data.

(14) The *anti*/*syn* refers the relationship between C2 and C3 bearing the phenylsulfanyl group.

(15) The ratio of *anti* to *syn* of these four isomers of **4** were alternatively determined by deoxygenation through treatment with diimidazolylmethane-1-thione and then tributyltinhydride-AIBN to the two diastereomers that were then treated with *m*CPBA followed by thermal *syn*-elimination to afford *E*- and *Z*-olefins, methyl 2-benzylbut-2-enoate in the same ratio of 74 : 26.

(16) The ratio of four isomers **4a** was determined by NMR to be 69 : 20 : 8 : 3, corresponding to 89 : 11 for *anti*- to *syn*-**4a**. The stereochemistry around the OH function was determined according to the reported coupling constant (**A**, **D**: ca. 5 Hz; **B**, **C**: 7-9 Hz). Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *29*, 4292-4299. The numbers in parentheses are the diastereomeric ratio based on the C2 and C-OH centers, corresponding to the structures, the most major **A** to the most minor **D**.



(17) General procedure (Table 1, entry 6): A solution of **1a** (1.0 mmol) and pivalaldehyde (2.0 mmol) in toluene (1.5 mL) was added to a mixture of PhSTMS (2.0 mmol) and 0.2 mmol of PhSLi, prepared from PhSH and BuLi, in toluene (2 mL). After stirring for 16 h at rt, the reaction was quenched with aq. ammonium chloride and extracted with ethyl acetate. Concentration gave an oil that was treated with 10% HCl (5 mL) in THF (5 mL) for 15 min at rt. The mixture was diluted with water and extracted with ethyl acetate. Concentration and silica gel column chromatography (benzene-ethyl acetate, 9 : 1) gave diastereomerically pure **4** (R^1 = Me, R^2 = *t*-Bu; Scheme 5) in 83% yield.

(18) 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.