Tandem Michael–Aldol Reaction

Asymmetric Induction of Three Consecutive Chiral Centers by Reactions of *N*-Enoylthioamides with Aldehydes**

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Recently we developed a chalcogenide/$TiCl_4$-mediated reaction, which consists of the Michael addition of a chloride ion generated from a chalcogenide/$TiCl_4$ complex to an enone, followed by an aldol reaction with an aldehyde to give an α-chloromethyl aldol, which can be transformed into an α-methylene aldol (the Morita–Baylis–Hillman adduct).[1,2] This reaction is completed much faster than the Morita–Baylis–Hillman reaction[3] and, therefore, can be utilized advantageously in several reactions which do not give good results under Morita–Baylis–Hillman reaction conditions.[4–8] We further studied the tandem Michael–aldol reaction initiated by the intramolecular Michael cyclization of a chalcogenide group to an enone moiety.[9–11] Goodman et al. reported a similar intermolecular example.[12]

While investigating the chalcogenide catalyst, we found that a thioketone acted as a nucleophile toward an enone[13] and a thiourea was also useful for the tandem Michael–aldol reaction.[14] Recently, it was reported that a thiourea moiety added intramolecularly to an enone moiety to form a thiazine ring.[15,16] These reports prompted us to examine the tandem Michael–aldol reaction of *N*-propenoyl cyclic thioamides with aldehydes. We now report the asymmetric tandem Michael–aldol reaction of chiral *N*-cinnamoyl-1,3-thiazolidine-2-thione and its 1,3-oxazolidine congener with aldehydes in the presence of $BF_3{\cdot}Et_2O$.

The reaction of *N*-cinnamoyl-1,3-thiazolidine-2-thione (**1a**) with *p*-chlorobenzaldehyde (**2a**) was conducted for the first time [Eq. (1)]. The results are shown in Table 1. Various molar ratios of the starting compounds and the Lewis acid were tested, and the best result was obtained from the reaction of **1a** (2 equiv) with **2a** (1 equiv) in the presence of 3 equiv $BF_3{\cdot}Et_2O$ (Table 1, entry 1). This reaction was quite fast and was completed within 15 minutes at room temper-

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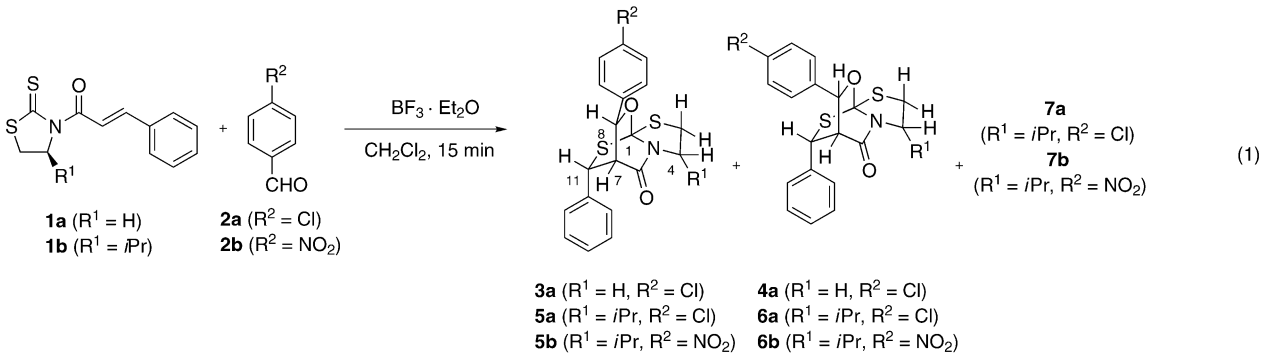


Table 1: Representative results for the screening of reaction conditions for the diastereoselective tandem Michael–aldol reactions of *N*-cinnamoyl-1,3-thiazolidine-2-thiones **1a**,**b** with aldehydes **2a**,**b**.

Entry	Enone (equiv)	Aldehyde (equiv)	$BF_3{\cdot}Et_2O$ [equiv]	*T*	Products[a] (% yield)
1	**1a** (2)	**2a** (1)	3	RT	**3a** (58), **4a** (31)
2	**1a** (2)	**2a** (1)	2	RT	**3a** (50), **4a** (33)
3	**1a** (1)	**2a** (2)	3	RT	**3a** (48), **4a** (30)
4	**1b** (2)	**2a** (1)	3	0 °C	**5a** (54), **6a** (28), **7a** (4)
5	**1b** (2)	**2b** (1)	3	0 °C	**5b** (43), **6b** (41), **7b** (4)

[a] Minor products **7a** and **7b** have the same molecular weights and composition formulas, $C_{22}H_{22}ClNO_2S_2$ and $C_{22}H_{22}N_2O_4S_2$, as **5a**, **6a** and **5b**, **6b**, respectively, but the amounts of **7a** and **7b** are so small that their stereostructures could not yet be determined.

ature. The structures of products **3a** and **4a** were determined by comparing the their ^1H and ^{13}C NMR data with those of **5a**, whose structure was elucidated by X-ray analysis (vide infra).

We obtained the three diastereomeric products **5**–**7** from the reactions of chiral thioamide **1b**, which has a 4*S* configuration, with aldehydes **2a**,**b**. X-ray analysis revealed that the major product **5a** ($R^1 = iPr$, $R^2 = Cl$) has a tricyclic ring system, in which a chiral bridgehead carbon is bound to four heteroatoms (Figure 1). The configuration of the four chiral centers is 1*R*,4*S*,7*R*,8*S*,11*R*.[17] The structure of product **6a**, in which the ClC_6H_4 group is on the same side as H-11, was determined by comparing its ^1H and ^{13}C NMR spectra with those of **5a**. The absolute configuration of the 8-position is 8*R*, opposite to that of **5a**.

Palomo et al. reported that a chiral thioamide can undergo an asymmetric Michael addition to an intramolecular enone moiety with high diastereoselectivity.[16] Based on their findings and ours, we anticipated that the stereoselective formation of the four chiral centers involving three consecutive chiral carbons could be achieved if the aldol reaction of an enolate with an aldehyde could be stereocontrolled. Hence, we selected 4,5-disubstituted oxazolidine-2-thione as a chiral auxiliary and carried out reactions of *N*-cinnamoyl-4*S*-methyl-5*R*-phenyloxazolidinethione (**1c**) with various aldehydes [Eq. (2)] (Table 2).

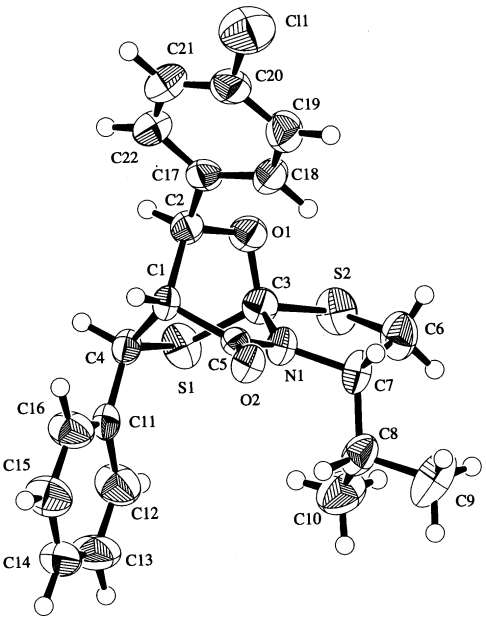
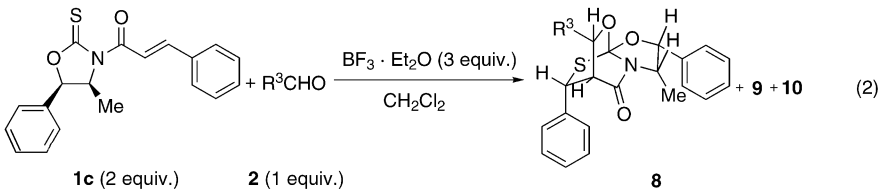


Figure 1. X-ray crystal structure of **5a** (ORTEP drawing).



The best molar ratio of enone **1** and aldehyde **2** from Table 1 was applied to the reaction of **1c** and **2b**, and the reaction temperature and time were examined. The reaction at −78 °C for 25 h gave **8b** in 27 % yield (Table 2, entry 1). When the reaction was conducted at −40 °C, the chemical yield increased but a small amount of diastereomer **9b** formed (entry 2). The best result was obtained for the reaction at −40 °C for 24 h (entry 3). The stereostructure of

Table 2: Diastereoselective tandem Michael–aldol reactions of *N*-cinnamoyl-1,3-oxazolidine-2-thione **1c** with aldehydes **2a**–**e**.

Entry	Aldehyde (R^3)	Conditions	Yield [%][a]	**8**:**9**:**10**[b]
1	**2b** (p-$NO_2C_6H_4$)	−78 °C, 25 h	27	100:0:0
2	**2b** (p-$NO_2C_6H_4$)	−40 °C, 5 h	77	94:6:0
3	**2b** (p-$NO_2C_6H_4$)	−40 °C, 24 h	93	95:5:0
4	**2c** (m-$NO_2C_6H_4$)	−40 °C, 24 h	85	95:5:0
5	**2a** (p-ClC_6H_4)	−40 °C, 24 h	71	86:7:7
6	**2d** (Ph)	0 °C, 1 h	69	69:3:28
7	**2e** (p-MeC_6H_4)	0 °C, 1 h	59	92:0:8

[a] Mixture of diastereoisomers. [b] HRMS data indicate that products **9** and **10** have the same molecular formulas as product **8**, but their sterostructures could not be determined because of the small amounts.

the major product **8b** corresponds to that of **6b,** which has a 4-isopropylthiazolidine moiety. Diastereomer ratios of the products were determined from ^{1}H NMR spectra of the crude products. Reactions with *p*-chloro- (**2a**) and *m*-nitrobenzaldehyde (**2c**) were conducted similarly and gave products **8a** and **8c** in good yields together with isomers **9a**,**c** and **10a** (entries 4 and 5). The reaction with benzaldehyde was slow and was conducted at 0 °C, but the diasteromer ratio was decreased (entry 6). Reaction with *p*-tolualdehyde (**2e**) gave the products in a moderate chemical yield (entry 7). The reaction with *o*-nitrobenzaldehyde was very slow because of the steric hindrance, and the reaction with dihydrocinnamaldehyde gave a mixture of products with a low diastereomer ratio.

In conclusion, we have developed a novel tandem Michael–aldol reaction of chiral thioamide-enones with aldehydes, which induces four chiral centers simultaneously. This method is easy to use and gives unusual heterotricyclic compounds with three consecutive chiral centers and a chiral carbon center bound to four heteroatoms. If the products can be converted into polyfunctionalized chiral carboxylic acids, aldehydes, amides or alcohols, they can be widely utilized for organic synthesis. This is the subject of current investigation.

Experimental Section

General procedure: To a stirred solution of (4*S*,5*R*)-4-methyl-5-phenyl-3-[(*E*)-3-phenylprop-2-enoyl]-1,3-oxazolidine-2-thione (**1c**)(323 mg, 1.0 mmol) and *p*-nitrobenzaldehyde (**2b**)(76 mg, 0.5 mmol) in dry CH_2Cl_2 (1.6 mL) was added dropwise a solution of $BF_3{\cdot}Et_2O$ (190 μL, 1.5 mmol) at −40 °C. The mixture was stirred at the same temperature for 24 h, poured into $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by recycling preparative HPLC, eluting with chloroform to give **8b** and **9b**.

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[17] Crystal structure data for **5a**: $C_{22}H_{22}ClNO_2S_2$, $M_r = 431.99$, prismatic, space group $P2_12_12_1$, $a = 11.636(2)$, $b = 18.035(2)$, $c = 9.947(2)$ Å, $V = 2087.4(5)$ Å^3, $T = 296$ K, $Z = 4$, $\rho_{calcd} = 1.375$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 4.01$ cm^{-1}, $R = 0.0243$, $R_w = 0.061$. CCDC-200264 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

