

# A C–C bond formation reaction at the $\alpha$ -carbon atom of $\alpha$ -oxo ketene dithioacetals via the Baylis–Hillman type reaction

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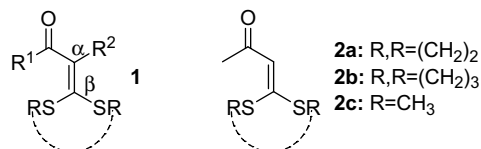
**Abstract**—The first example of  $\text{TiCl}_4$ -mediated Baylis–Hillman type reaction of  $\alpha$ -acetyl cyclic ketene dithioacetals with arylaldehydes was described. This methodology adds a new entry to the C–C bond formation at the  $\alpha$ -carbon atom of  $\alpha$ -oxo ketene dithioacetals.

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As a kind of versatile synthons,  $\alpha$ -oxo ketene dithioacetals **1** have found their wide utilizations in organic synthesis, especially in the synthesis of various aromatic and heterocyclic compounds.<sup>1,2</sup> Compared with the numerous reports involved in the reactions in which  $\alpha$ -oxo ketene dithioacetals were taken as 1,3-electrophiles, the research relevant to the reaction at their  $\alpha$ -carbon atom was poorly investigated. It is clear that the highly polarized push (RS)–pull ( $\text{R}^1\text{CO}$ ) interaction on the C=C double bond of these,  $\beta,\beta$ -dialkylthio- $\alpha,\beta$ -enones and analogues makes their  $\alpha$ -carbon atom a potential nucleophilic centre. Accordingly, the  $\alpha$ -functionalization reaction of **1** has been developed in our group very recently.<sup>3</sup> Some heteroatom functional groups such as Br, I and  $\text{NO}_2$  have been successfully introduced into the  $\alpha$ -position of the appropriate **1** ( $\text{R}^2 = \text{acetyl}$  or carboxyl) via halodecarboxylation or similar reaction.<sup>3</sup>

With the aim to establish a new method for the C–C bond formation at the  $\alpha$ -carbon atom of  $\alpha$ -oxo ketene dithioacetals, on our ongoing research,<sup>4</sup> we have become interested in investigating the reactivity of compounds **2** towards carbon electrophiles.

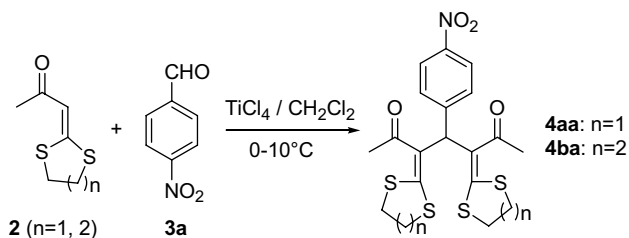
Based on the C–C coupling of activated alkenes (at the  $\alpha$ -position) with a carbon electrophile, the Baylis–Hillman (BH) reaction<sup>5</sup> can provide various polyfunctionalized molecules and has been applied to the synthesis of various biologically active compounds and natural products.<sup>6</sup> As a kind of special alkenes with electron rich  $\alpha$ -carbon atom, compounds **2** are expected to proceed more efficiently than those employed in the BH reaction. However, the alkenes bearing  $\beta$ -substituent(s) have been usually proven to be inert due to the steric hindrance towards the attack of the base in the BH reaction.<sup>5</sup> To circumvent this problem, a number of attempts have been made to provide the BH adducts including the use of some BH type reactions.<sup>7</sup> Recently, we found an unprecedented BH type reaction between  $\alpha$ -oxo ketene dithioacetals **2** and arylaldehydes and the experimental results are described in this letter.



**Keywords:**  $\alpha$ -Oxo ketene dithioacetals; Activated alkenes; C–C Bond formation; Baylis–Hillman type reaction; Double Baylis–Hillman products.

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In our preliminary experiment, the reaction of **2a** with 4-nitrobenzaldehyde **3a** (1.0 equiv) in the presence of DABCO (1–10 equiv) was attempted. Unfortunately, when the reaction was performed in anhydrous  $\text{CH}_2\text{Cl}_2$  at room temperature, no reaction occurred after 3 days and only **2a** and **3a** were recovered, respectively. Similarly, DBU and  $\text{Et}_3\text{N}$  were also proven to be the



Scheme 1. The reaction of **2** and **3a** mediated by  $\text{TiCl}_4$ .

inefficient basic catalysts for this reaction. According to the mechanism of the amine-catalyzed BH reaction, the steric hindrance of the  $\beta,\beta$ -dialkylthio groups of **2a** should be the reason for why the above reaction was inert under the typical BH conditions.<sup>5</sup>

We then turned to the acidic catalysts and  $\text{TiCl}_4$  was chosen to promote the reaction of **2a** with **3a** with the consideration that the carbonyl group of an aldehyde was prone to be more electrophilic under the activation by the Lewis acid. Indeed, when the reaction was carried out in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 mL) at 0–10 °C for 2 days, the double BH product **4aa** was isolated in 35% yield with 55% recovery of **3a** (Scheme 1).

Since the one-pot synthesis of **4aa** presented the first example of the double BH type reaction, the reaction conditions were then examined in detail. By changing the ratio of **2a**:**3a** from 1:1 to 6:1 with a constant amount of  $\text{TiCl}_4$  (1.2 equiv), it was found that the ratio of **2a**:**3a** showed significant effect not only on the product yield but also on the reaction rate. With the optimized ratio of **2a**:**3a** (4:1), **4aa** was obtained in 72% isolated yield and the reaction time was shortened to 7 h. Under the identical conditions, **4ba** was obtained in 65% yield from the reaction of **2b** and **3a** and its structure was established by a single crystal X-ray diffraction study (Fig. 1).<sup>8</sup> Interestingly, under the identical conditions, no reaction occurred between **2c** and **3a**.

As expected to extend the scope of this novel reaction, the selected aldehydes, such as arylaldehydes with elec-

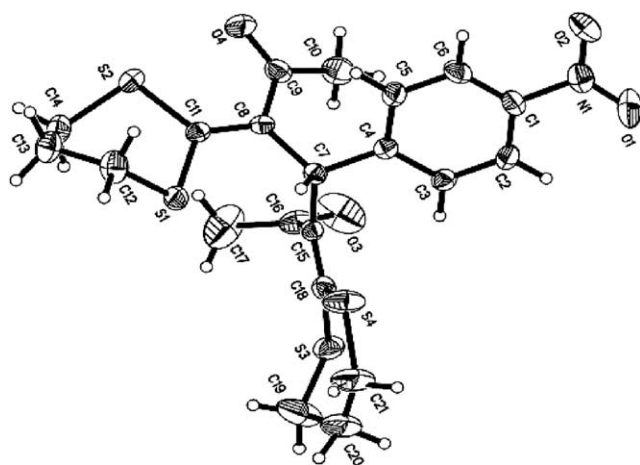
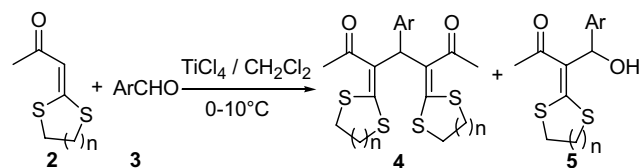


Figure 1. The crystal structure of **4ba**.



Scheme 2. The reaction of **2** and **3** in the presence of  $\text{TiCl}_4$ .

Table 1. The reaction of **2** and **3** in the presence of  $\text{TiCl}_4$ .<sup>a,b</sup>

Entry	<b>2</b>	<b>3</b>	<i>n</i>	Ar	Time (h)	Product	Yield <sup>c</sup> (%)
1	<b>2a</b>	<b>3a</b>	1	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	7	<b>4aa</b>	72
2	<b>2b</b>	<b>3a</b>	2	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	8	<b>4ba</b>	65
3	<b>2a</b>	<b>3b</b>	1	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	9	<b>4ab</b>	69
4	<b>2b</b>	<b>3b</b>	2	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	10	<b>4bb</b>	66
5	<b>2a</b>	<b>3c</b>	1	4-ClC <sub>6</sub> H <sub>4</sub>	12	<b>4ac</b>	49
6	<b>2a</b>	<b>3d</b>	1	4-CHOC <sub>6</sub> H <sub>4</sub>	9	<b>4ad</b>	54
7	<b>2a</b>	<b>3e</b>	1	4-FC <sub>6</sub> H <sub>4</sub>	18	<b>4ae</b>	44
8	<b>2a</b>	<b>3f</b>	1	C <sub>6</sub> H <sub>5</sub>	30	<b>4af</b>	32
9 <sup>d</sup>	<b>2a</b>	<b>3a</b>	1	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	2	<b>4aa</b>	24
						<b>5aa</b>	23
10 <sup>e</sup>	<b>2a</b>	<b>3d</b>	1	4-CHOC <sub>6</sub> H <sub>4</sub>	1	<b>4ad</b>	20
						<b>5ad</b>	28

<sup>a</sup> Reaction conditions: **2** (2 mmol), **3** (0.5 mmol),  $\text{TiCl}_4$  (0.6 mmol),  $\text{CH}_2\text{Cl}_2$  (10 mL), 0–10 °C.

<sup>b</sup> All products **4** and **5** were characterized by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and elemental analysis.

<sup>c</sup> Isolated yields.

<sup>d</sup> **2a**:**3a** = 1:3.

<sup>e</sup> **2a**:**3d** = 1:3.

tron-withdrawing/donating groups, and aliphatic aldehyde (pivalaldehyde), were tried under the above conditions (Scheme 2). The results were summarized in Table 1.<sup>9</sup> Based on these results, it was clear that arylaldehydes with strong electron-withdrawing group led to increased yields and shortened reaction time. Comparatively, for arylaldehydes with electron-donating group, that is, 4-methylbenzaldehyde and 4-methoxybenzaldehyde, only trace amounts of the double BH products were found according to the <sup>1</sup>H NMR analysis of the reaction mixture after recovery of the substrates. For the case of pivalaldehyde, no reaction occurred even when the reaction time was prolonged to 3 days. In our experiment, it was also observed that there was limited influence on both the yield and the reaction rate when the amount of  $\text{TiCl}_4$  was varied from 1.0 to 2.0 mol equiv. However, 0.5 mol equiv of  $\text{TiCl}_4$  was proven not enough to complete this double BH type reaction.

It was found, by TLC monitoring of the reaction progress of **2a** with **3a** that the BH adduct **5aa** (according to <sup>1</sup>H NMR analysis of the reaction mixture) was also produced as a minor product. To obtain the BH adduct in pure form and to understand the reaction mechanism, arylaldehydes with strong electron-withdrawing groups, such as 4-nitrobenzaldehyde **3a** and terephthalaldehyde **3d**, were selected again to react with **2a** with the consideration that the BH adducts derived from them might be relatively stable to be trapped under an appropriate

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