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A C–C bond formation reaction at the α-carbon atom of α-oxo ketene dithioacetals via the Baylis–Hillman type reaction

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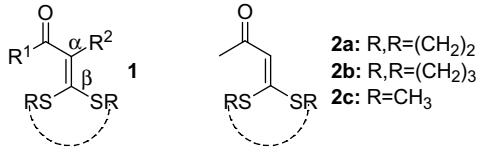
Abstract—The first example of $TiCl_4$-mediated Baylis–Hillman type reaction of α-acetyl cyclic ketene dithioacetals with arylaldehydes was described. This methodology adds a new entry to the C–C bond formation at the α-carbon atom of α-oxo ketene dithioacetals.

As a kind of versatile synthons, α-oxoketene dithioacetals **1** have found their wide utilizations in organic synthesis, especially in the synthesis of various aromatic and heterocyclic compounds.[1,2] Compared with the numerous reports involved in the reactions in which α-oxo ketene dithioacetals were taken as 1,3-electrophiles, the research relevant to the reaction at their α-carbon atom was poorly investigated. It is clear that the highly polarized push (RS)–pull (R^1CO) interaction on the C–C double bond of these, β,β-dialkylthio-α,β-enones and analogues makes their α-carbon atom a potential nucleophilic centre. Accordingly, the α-functionalization reaction of **1** has been developed in our group very recently.[3] Some heteroatom functional groups such as Br, I and NO_2 have been successfully introduced into the α-position of the appropriate **1** (R^2 = acetyl or carboxyl) via halodecarboxylation or similar reaction.[3]



With the aim to establish a new method for the C–C bond formation at the α-carbon atom of α-oxo ketene dithioacetals, on our ongoing research,[4] 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 α-position) with a carbon electrophile, the Baylis–Hillman (BH) reaction[5] can provide various polyfunctionalized molecules and has been applied to the synthesis of various biologically active compounds and natural products.[6] As a kind of special alkenes with electron rich α-carbon atom, compounds **2** are expected to proceed more efficiently than those employed in the BH reaction. However, the alkenes bearing β-substituent(s) have been usually proven to be inert due to the steric hindrance towards the attack of the base in the BH reaction.[5] To circumvent this problem, a number of attempts have been made to provide the BH adducts including the use of some BH type reactions.[7] Recently, we found an unprecedented BH type reaction between α-oxo ketene dithioacetals **2** and arylaldehydes and the experimental results are described in this letter.

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 CH_2Cl_2 at room temperature, no reaction occurred after 3 days and only **2a** and **3a** were recovered, respectively. Similarly, DBU and Et_3N were also proven to be the

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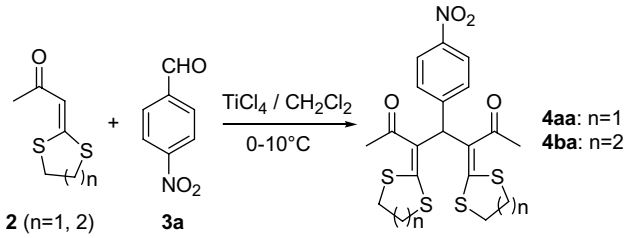


Scheme 1. The reaction of **2** and **3a** mediated by $TiCl_4$.

inefficient basic catalysts for this reaction. According to the mechanism of the amine-catalyzed BH reaction, the steric hindrance of the β,β-dialkylthio groups of **2a** should be the reason for why the above reaction was inert under the typical BH conditions.[5]

We then turned to the acidic catalysts and $TiCl_4$ 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 CH_2Cl_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 $TiCl_4$ (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).[8] 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 electron-withdrawing/donating groups, and aliphatic aldehyde (pivalaldehyde), were tried under the above conditions (Scheme 2). The results were summarized in Table 1.[9] 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-methoxylbenzaldehyde, only trace amounts of the double BH products were found according to the ^1H 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 $TiCl_4$ was varied from 1.0 to 2.0 mol equiv. However, 0.5 mol equiv of $TiCl_4$ was proven not enough to complete this double BH type reaction.

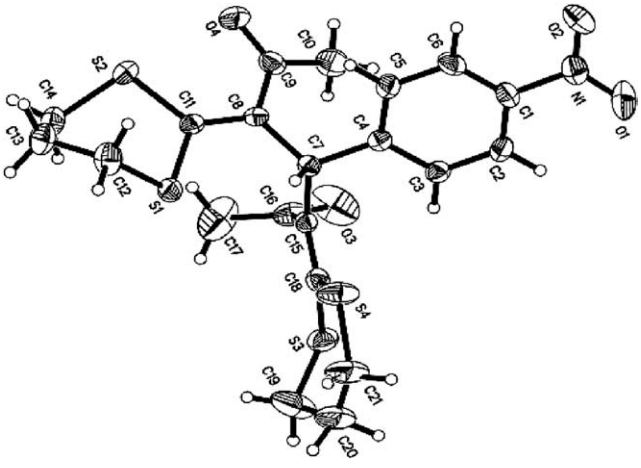
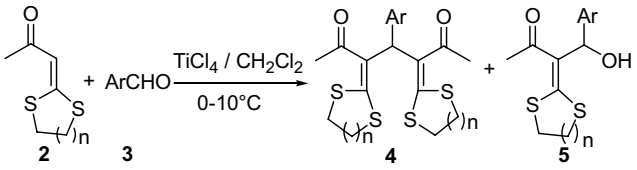


Figure 1. The crystal structure of **4ba**.



Scheme 2. The reaction of **2** and **3** in the presence of $TiCl_4$.

Table 1. The reaction of **2** and **3** in the presence of $TiCl_4$[a,b]

Entry	2	3	*n*	Ar	Time (h)	Product	Yield[c] (%)
1	**2a**	**3a**	1	4-$NO_2C_6H_4$	7	**4aa**	72
2	**2b**	**3a**	2	4-$NO_2C_6H_4$	8	**4ba**	65
3	**2a**	**3b**	1	3-$NO_2C_6H_4$	9	**4ab**	69
4	**2b**	**3b**	2	3-$NO_2C_6H_4$	10	**4bb**	66
5	**2a**	**3c**	1	4-ClC_6H_4	12	**4ac**	49
6	**2a**	**3d**	1	4-$CHOC_6H_4$	9	**4ad**	54
7	**2a**	**3e**	1	4-FC_6H_4	18	**4ae**	44
8	**2a**	**3f**	1	C_6H_5	30	**4af**	32
9[d]	**2a**	**3a**	1	4-$NO_2C_6H_4$	2	**4aa**	24
						5aa	23
10[e]	**2a**	**3d**	1	4-$CHOC_6H_4$	1	**4ad**	20
						5ad	28

[a] Reaction conditions: **2** (2 mmol), **3** (0.5 mmol), $TiCl_4$ (0.6 mmol), CH_2Cl_2 (10 mL), 0–10 °C.
[b] All products **4** and **5** were characterized by IR, ^1H NMR, ^{13}C NMR and elemental analysis.
[c] Isolated yields.
[d] **2a**:**3a** = 1:3.
[e] **2a**:**3d** = 1:3.

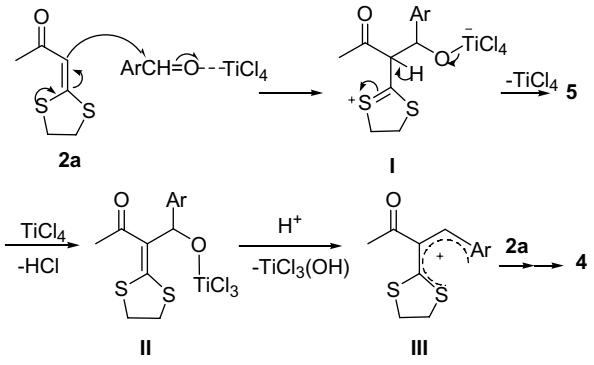
It was found, by TLC monitoring of the reaction progress of **2a** with **3a** that the BH adduct **5aa** (according to ^1H NMR analysis of the reaction mixture) was also produced as a minor product. To obtain the BH adduct in pure form and to understand the reaction mechanism, arylaldehydes with strong 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

condition. The experimental results revealed that the increased yield of the BH adduct could be obtained by increasing the amount of arylaldehyde and shortening the reaction time. In the 1:3 ratio of **2a**:**3a** under the identical conditions for 2 h, **4aa** (24%) and **5aa** (23%) were able to be separated by flash column chromatography (entry 9). Similarly, **4ad** and **5ad** were obtained in 20% and 28% yields, respectively (entry 10).

In order to understand the reaction mechanism, the BH adduct **5aa** was reacted with **2a** under the identical conditions and the double BH adduct **4aa** was obtained in 69% isolated yield. It should be mentioned that, neither the BH nor the double BH product was found when **4ad** was applied as the electrophile to examine its further reaction with **2a** under the same conditions. As the arylaldehyde bearing an electron-donating group on the aryl ring, this result indicated that **4ad** was not reactive towards **2a** under the reaction conditions.

Unlike the mechanism of the $TiCl_4$-catalyzed BH reaction,[10] which is believed to proceed through the Michael-initiated addition–elimination sequence, the stronger nucleophilicity of the α-carbon atom of **2** might require only electrophiles to be activated. Based on the experimental results mentioned above, the mechanism concerned was thus proposed and depicted in Scheme 3 (with **2a** as an example).

Initiated by the nucleophilic attack of the electron rich α-carbon atom of **2a** at the carbonyl carbon of the activated aldehyde, the BH adduct **5** was first produced via intermediate **I**. And then the double BH product **4** was formed from the reaction of intermediate **III** and **2a** with the aid of $TiCl_4$. Combining the experimental results with the proposed mechanism, it was indicated that: (1) the reaction of **2a** with arylaldehydes should be the rate determination step, and (2) the easy formation of the double BH product was probably due to the higher stability of the carbocation intermediate **III** from the delocalization of the positive charge by the bialkylthio sulfur atoms. The activated alkene **2b** possessed the similar property to **2a**. The inert of **2c** to this process may be due to the deactivated effect by the formation of a complex between $TiCl_4$ with the lone pair electrons of the sulfur atoms of **2c** because, unlike the rigid cyclic **2a** and **2b**, the carbon sulfur bond between sulfur atom and β-carbon atom is flexible.



Scheme 3. Proposed mechanism.

Recently, Minami and co-workers found a Lewis acid-promoted deoxygenative di[β,β-bis(ethylthio)]vinylation of silylketene diethylthioacetal with aldehydes.[11] Compared with the electron rich alkene with the three electron-donating groups used in Minami's research, the alkenes with electron rich α-carbon atom employed in our work are polarized by the stronger push (RS)–pull (R^1CO) interaction on the C–C double bond and are apt to the BH type reaction in the presence of Lewis acids.

In conclusion, we have described a novel Baylis–Hillman type reaction between α-oxoketene dithioacetals and arylaldehydes leading to the polyfunctionalized 1,4-pentadienes.[12] As far as we know, this is the first example in which the activated alkenes having two β,β-dialkylthio substituents are investigated in the BH reaction and similar processes. This research represents a new methodology for the C–C bond formation at the α-carbon atom of α-oxo ketene dithioacetals. Further investigation on this process and the application of the double BH products are in progress in our laboratory.

Acknowledgements

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8. *Crystal data* for **4ba**: $C_{21}H_{23}NO_4S_4$, colourless, M = 481.64, orthorhombic, space group *Pca*2(1), a = 12.458(3), b = 9.946(2), c = 18.149(4) Å, V = 2248.7(8) Å^3, μ = 0.451 mm^{-1}, Z = 4, T = 293 K, F_{000} = 1008, R = 0.0337, wR^2 = 0.0585. The CCDC deposition number: 245727.
9. *General procedure for the Baylis–Hillman type reaction of* **2** *and* **3**: To a solution of **2a** (4.0 mmol) and **3a** (1.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise $TiCl_4$ (1.2 mmol) via syringe for 1 min. at 0 °C. The mixture was allowed to react at 0–10 °C for 7 h till **3a** was consumed (monitored by TLC). Then the reaction was quenched by $NaHCO_3$ saturated aqueous solution (10 mL) leading to the white precipitate, which was filtered off afterwards. The filtrate was extracted with CH_2Cl_2 (10 mL × 2) and the organic layer was dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash silica gel chromatography to give compound **4aa** as a light yellow crystal (eluent: petroleum ether/ether = 3/1, V/V) in 72% yield. Compounds **4ba**, **4ab**, **4bb**, **4ac**, **4ad**, **4ae** and **4af** could also be formed after the corresponding time mentioned in Table 1 under the similar reaction conditions. When the reaction time was controlled within 2 h and using the 1:3 ratio of **2**:**3** under the identical conditions, the BH adducts **5aa** and **5ad** could also be obtained in 23% and 28% yields, respectively, besides the double BH products **4aa** (24%) and **4ad** (20%). Compound **4aa**: Light yellow crystal; mp: 162–164 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.93 (s, 6H), 3.28–3.30 (m, 8H), 5.78 (s, 1H), 7.39 (d, J = 7.5 Hz, 2H), 8.15 (d, J = 7.5 Hz, 2H);^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.7, 32.1, 32.6, 48.7, 118.3, 118.7, 124.7, 141.7, 143.6, 159.1, 189.8; IR (KBr): 2924, 1678, 1631, 1516, 1455, 1347, 1238 cm^{-1}; Anal. Calcd for $C_{19}H_{19}NO_4S_4$: C 50.31, H 4.22, N 3.09. Found C 50.23, H 4.15, N 2.98. Compound **5aa**: White crystal; mp: 158–160 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.07 (s, 3H), 3.08 (d, J = 4.5 Hz, 1H), 3.36–3.47 (m, 4H), 6.21 (d, J = 4.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 8.20 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 29.2, 36.1, 39.1, 74.4, 123.6, 126.4, 126.5, 147.1, 149.1, 166.2, 195.0; IR (KBr): 3446, 2925, 1621, 1518, 1458, 1344, 1245 cm^{-1}; Anal. Calcd for $C_{13}H_{13}NO_4S_2$: C 50.15, H 4.21, N 4.50. Found C 50.38, H 4.17, N, 4.58.
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