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# Lewis acid-promoted Baylis–Hillman-type reaction of α,β-unsaturated ethyl thioester with aldehydes without the use of a Lewis base†

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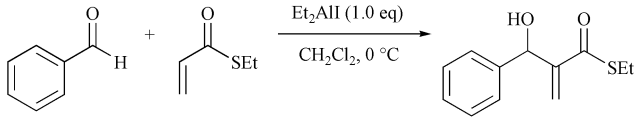
**The Baylis–Hillman-type reaction of α,β-ethyl thioacrylate with aldehydes has been achieved using diethylaluminium iodide as the promoter without the direct use of any Lewis bases. The reaction provides an effective access to various α-methylene-β-hydroxy thioesters.**

The study of Baylis–Hillman and related C($sp^3$)–C($sp^2$) bond formations has become an active topic in organic chemistry.[1–3] So far, almost all of the Baylis–Hillman-type reactions require the direct use of Lewis bases, such as DABCO, $Ph_3P$ and chalcogen species.[4,5] It is rare for these reactions not to involve any Lewis bases. Recently, we reported that $TiCl_4$ can promote the Baylis–Hillman reaction in the absence of these Lewis bases when α,β-unsaturated cycloketones serve as the Michael-type acceptors.[6,7] We also found when α,β-unsaturated *N*-benzoxazolinone was subjected to the reaction at room temperature, the reaction can be controlled at the stage of forming β-chloro aldols.[6a] However, when the substrates were changed to α,β-unsaturated acyclic ketones, the reaction smoothly proceeded to give (*Z*)-2-(halomethyl)vinyl ketones.[3a] These reactions have also been carried out by using Lewis acid/Lewis base co-promoters under different conditions.[8]

We next attempted to utilize α,β-unsaturated alkyl esters for the $TiCl_4$-promoted Baylis–Hillman reaction in the absence of the above Lewis bases. But the success was very limited. After screening a variety of Lewis acid halides (*e.g.*, $AlCl_3$, $BCl_3$, $TiBr_4$ and $Et_2AlI$) under different conditions, we found that α,β-unsaturated ethyl thioacrylate can undergo the Baylis–Hillman reaction using diethylaluminium iodide alone as the promoter. The reaction proceeded smoothly at 0 °C in dichloromethane as shown in Scheme 1 with the results summarized in Table 1.

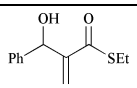
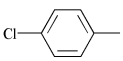
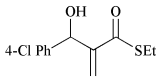
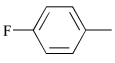
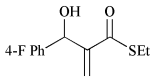
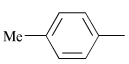
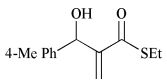
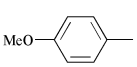
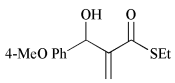
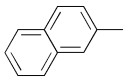
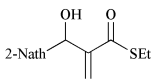
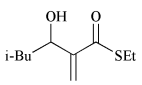
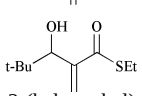
Scheme 2 outlines the mechanistic hypothesis. We believe that the irreversible deprotonation at step C is responsible for the success of using α,β-unsaturated thioesters which belong to a difficult substrate class for the Baylis–Hillman reaction. Release of $CH_3CH_3$ acts as a strong driving force thus making the reaction irreversible. This step benefits both the chemical yields and the reaction rate. This hypothesis can also distinguish diethylaluminium iodide[9] from other Lewis acids examined which gave either no Baylis–Hillman adducts or a trace amount of these products. In the system of the α,β-unsaturated cycloketone–$TiCl_4$ combination, the first step is the intermolecular Michael-type addition, which is governed by the rigid characteristic of α,β-unsaturated cycloketones. But in this




**Scheme 1**

† Electronic supplementary information (ESI) available: experimental data for **1**–**8**. See http://www.rsc.org/suppdata/cc/b2/b204210j/

**Table 1** Results of $Et_2AlI$-mediated B–H type reaction[10]

| Entry | R- | Product | | Chemoselectivity[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  |  | **1** | 6:1 | 64 |
| 2 |  |  | **2** | 8:1 | 73 |
| 3 |  |  | **3** | 4:1 | 60 |
| 4[c] |  |  | **4** | 4:1 | 65 |
| 5[c] |  |  | **5** | 3:1 | 60 |
| 6[c] |  |  | **6** | 6:1 | 75 |
| 7[c] |  |  | **7** | 3:2 | 54 |
| 8[c] |  |  | **8** | > 20:1 | 83 |

[a] Determined by crude $^1$H-NMR analysis, > 20:1 means (*Z*)-2-(halomethyl)vinyl thioester was not observed; [b] Purified yields of Baylis–Hillman adducts after column chromatography. [c] The reaction was carried out for 20 h.

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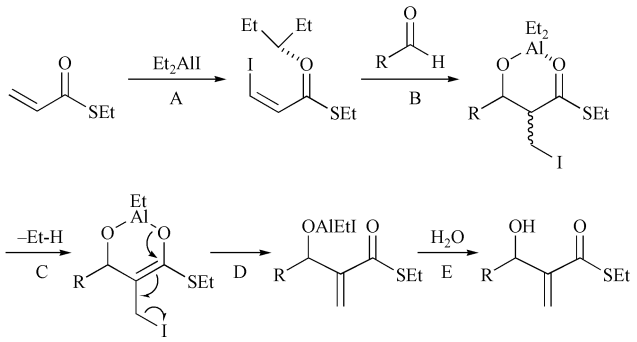


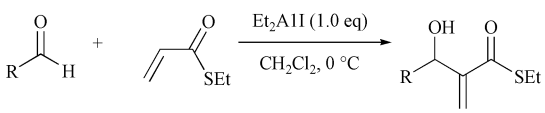
**Scheme 2**

new system, it is more likely for the Michael-type addition to occur through an intramolecular pathway due to the flexible structure of the α,β-unsaturated thioester (Scheme 2). This intramolecular pathway is similar to that of haloaldol reaction promoted by $TiCl_4$-*n*$Et_4NI$ as proposed by Oshima and co-workers.[8a]

Interestingly, the current system did not work well for normal α,β-unsaturated esters. In these cases, α-iodomethyl aldols instead of α-methylene-β-hydroxy thioesters are predominantly generated. This situation is attributed to the fact that the ester group is a stronger electron-withdrawing group which can stabilize the enolate anion better than the thioester group. Such stabilization makes the elimination (step D) unfavorable. Therefore, the thioester group plays a crucial role for the success of this new reaction system.

As shown in Scheme 1, the new reaction can be performed simply by mixing the aldehyde, α,β-unsaturated thioester and diethylaluminium iodide in dichloromethane at 0 °C. The reaction went to completion at this temperature within 7 h for several cases (cases 1–3 of Table 1), in comparison to the previous chalcogeno-Baylis–Hillman system[5] in which the mixture of $TiCl_4$ and $Me_2S$ was utilized at room temperature as the promoter and the catalyst, respectively. The previous reaction requires an excess amount of α,β-unsaturated ethyl thioacrylate (2.0 equiv.) for the complete consumption of aldehydes. In addition, the chalcogeno-Baylis–Hillman reaction gave a mixture of products consisting of the Baylis–Hillman adduct and α-halomethyl aldol. This side product needs further treatment with an excess amount of $Ti(OPr\text{-}i)_4$ or DBU to be converted into α-methylene-β-hydroxy thioesters *via* the elimination mechanism. Very interestingly, under the new conditions, (*Z*)-2-(iodomethyl)vinyl thioester was obtained as the major side product without the formation of α-halomethyl aldol.

One equivalent of $Et_2AlI$ is proven to be necessary to minimize the generation of (*Z*)-2-(iodomethyl)vinyl thioester. When a substoichiometric amount of diethylaluminium iodide (0.5 equiv.) was used, the reaction could also be furnished within the same period of time, but the ratio of the Baylis–Hillman adduct to (*Z*)-2-(iodomethyl)vinyl thioester was diminished to 1 : 1. The use of an excess amount of $Et_2AlI$ did not give any improvement in both yield and chemoselectivity. Low temperature (0 °C) is also necessary. In fact, when the reaction is carried out at room temperature, more of the side product is observed.



Obviously, the new system has the advantages of simple operation and faster reaction rate. For benzaldehyde and 4-chlorobenzaldehyde (entry 1 and 2 of Table 1), yields of 64 and 73% were obtained as compared to the chalcogeno-Baylis–Hillman conditions which gave 50 and 70% yields, respectively, for the same substrates. The new reaction also showed good chemoselectivity for most cases. But at the current stage, it is not clear why for the two nonaromatic cases (cases **7** and **8** of Table 1) the chemoselectivity differs so much ( > 20 : 1 for **8** and only 3 : 2 for **7**).

This new reaction showed a good scope of aldehyde substrates. Both aromatic and aliphatic aldehydes can be used as the electrophilic acceptors to react with aluminium enolate intermediates derived from conjugate addition of $Et_2AlI$ onto α,β-unsaturated thioester. Although the substitutions on aromatic rings did not have an obvious effect on yields for aromatic aldehydes, the two electron-donating substitutions (**4** and **5** of Table 1) seem to increase the formation of (*Z*)-2-(iodomethyl)vinyl thioester side products. It should be noted that this communication demonstrates the first examples for the synthesis of electron-donating aromatic Baylis–Hillman thioesters. α,β-Unsaturated aldehydes have also been used as electrophiles, but poor yields (less than 40%) were obtained with about the same amount of (*Z*)-2-(iodomethyl)vinyl thioester as the side product.

In summary, the Baylis–Hillman-type reaction of α,β-unsaturated ethyl thioacrylate with various aldehydes has been achieved without involving any Lewis bases. The reaction has a good substrate scope and provides a more effective and milder approach to a variety of Baylis–Hillman thioesters.

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