

# A remarkable rate acceleration of the Baylis–Hillman reaction

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Treatment of  $\alpha$ -naphthyl acrylate with both aliphatic and aromatic aldehydes in the presence of DABCO (30 mol%) afforded the desired ( $\alpha$ -methylene- $\beta$ -hydroxy)esters with reasonable chemical yields (51–88%) within 20 min.

Increasing interest has been focused on the coupling of an aldehyde with acrylate in the presence of DABCO (Baylis–Hillman reaction).<sup>1</sup> The resulting ( $\alpha$ -methylene- $\beta$ -hydroxy)-esters are versatile intermediates that allow for further functional group manipulation. One of the major drawbacks of this transformation is the poor reaction rates which limits the range of substrates that are tolerated.<sup>2</sup> Many aromatic aldehydes and branched aliphatic aldehydes are reluctant to serve as substrates. It is not surprising that numerous methods including physical as well as chemical attempts have been made to increase the reaction rate.<sup>3</sup> Modest increases in rates have been obtained under modified reaction conditions. No practical methods have been developed so far. We wish to report here that an extremely rapid rate can be achieved using  $\alpha$ -naphthyl acrylate as the Michael acceptor for the Baylis–Hillman reaction.

A plausible mechanism for the Baylis–Hillman reaction is proposed and the addition of ammonium enolate with an aldehyde is believed to be the rate-determining step.<sup>4</sup> Stabilization of the enolate species would shift the equilibrium forward and therefore to accelerate the rates. The use of Lewis acid to catalyze this transformation is a common strategy. The use of lanthanides and group III metal triflates to accelerate the Baylis–Hillman reaction have been studied.<sup>3e–g</sup> However structural variants of acrylates for this transformation have not been studied systematically.<sup>5</sup> This promoted us to screen a range of substituted acrylates **1a–g** as Michael acceptor. The substituted acrylates may provide stereo- and/or stereoelectronic effects to stabilize the oxy anion intermediate and subsequently accelerate the following aldol reaction. To test this hypothesis various acrylates **1a–g** with diverse steric, geometric and electronic properties were prepared and benzaldehyde was used as a probe electrophile (Table 1). Reaction of methyl acrylate (1.0 equiv.) with benzaldehyde (1.0 equiv.) in CH<sub>3</sub>CN in the presence of DABCO (50 mol%) at room temperature gave the corresponding product **2a** in 62% yield for 48 h (entry 1). The use of *tert*-butyl acrylate affords a similar result (entry 2). The use of phenyl acrylate **1c** gave the desired product **2c** with 86% yield in 2 h (entry 3). Treatment of benzyl acrylate with benzaldehyde under the same reaction conditions provided **2d** with 80% yield in 15 h (entry 4). The desired product **2e** was isolated in 34% yield when the commercial available 1,1,1,3,3,3-hexafluoroisopropyl acrylate<sup>6</sup> **1e** was used (entry 5). The use of  $\beta$ -naphthyl acrylate **1f** gave **2f** with 70% yield in 5 h (entry 6). A significant rate acceleration was observed when  $\alpha$ -naphthyl acrylate **1g** was employed. Thus, treatment of **1g** with benzaldehyde in the presence of DABCO affords the desired product with 88% yield in 20 min (entry 7). The unexpected rate acceleration using  $\alpha$ -naphthyl acrylate for the Baylis–Hillman reaction is amazing and was studied in more detail.

To further determine the feasibility of this system, various aldehydes were then studied using  $\alpha$ -naphthyl acrylate under the optimum conditions and the results are tabulated in Table 2. Thus, treatment of **1g** with acetaldehyde affords **3a** with 70%

yield at room temperature in 20 min (entry 1). Similar results were observed with different chain aldehydes (entries 2–4). The reaction was slightly less effective when  $\alpha$ -branched aldehyde was used (entry 5). *trans*-Cinnamaldehyde was employed to give the desired product with 60% yield in 20 min (entry 6). Next, substituted aromatic aldehydes were subjected to the same reaction conditions. Reaction of *p*-nitrobenzaldehyde and *p*-fluorobenzaldehyde with **1g** under the same conditions

**Table 1** Reaction of benzaldehyde with various acrylates **1a–g** in the presence of DABCO<sup>a</sup>

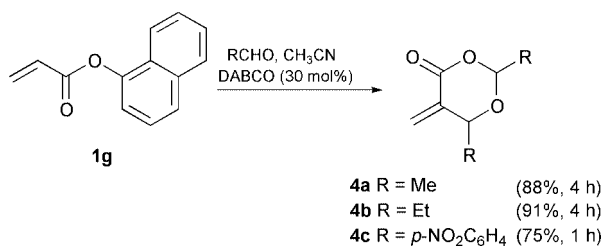
Entry	Acrylate	<i>t</i> /h	Product	Yield (%) <sup>b</sup>
1	<b>1a</b>	48 (4) <sup>c</sup>	<b>2a</b>	62 (68)
2	<b>1b</b>	15 (28 days) <sup>d</sup>	<b>2b</b>	50 (90)
3	<b>1c</b>	2 (3) <sup>e</sup>	<b>2c</b>	86 (78)
4	<b>1d</b>	15	<b>2d</b>	80
5	<b>1e</b>	48	<b>2e</b>	34
6	<b>1f</b>	5	<b>2f</b>	70
7	<b>1g</b>	1/3	<b>2g</b>	88

<sup>a</sup> All reactions were conducted using 1:1 ratio of acrylate and aldehyde in CH<sub>3</sub>CN at room temperature in the presence of DABCO (50 mol%).  
<sup>b</sup> Isolated yield. <sup>c</sup> Numbers in parentheses are reported data. For experimental details see ref. 3j. <sup>d</sup> Ref. 2. <sup>e</sup> Ref. 5.

**Table 2** Reaction of **1g** with various aldehydes<sup>a</sup>

Entry	RCHO (R=)	<i>t</i> /min	<b>3</b> (% yield) <sup>b</sup>
1	CH <sub>3</sub>	20	70
2	CH <sub>3</sub> CH <sub>2</sub>	20	77
3	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	20	62
4	PhCH <sub>2</sub> CH <sub>2</sub>	20	65
5	(CH <sub>3</sub> ) <sub>2</sub> CH	20	51
6	<i>trans</i> -C <sub>6</sub> H <sub>4</sub> CH=CH	20	60
7	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	10	82
8	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	20	65
9	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	20	71
10	<i>p</i> -OMeC <sub>6</sub> H <sub>4</sub>	20 h	35
11	<i>p</i> -OMeC <sub>6</sub> H <sub>4</sub>	96 h	71
12	3-Pyridyl	20	72

<sup>a</sup> All reactions were conducted using 1:1 molar ratio of acrylate and aldehyde in CH<sub>3</sub>CN at room temperature. The amounts of DABCO used was reduced to 30 mol% to minimize the formation of the cyclic acetates **4**.  
<sup>b</sup> Isolated yield.



**Scheme 1** The synthesis of 1,3-dioxan-4-ones **4a–c**.

provide the desired products with 82 and 65% yield, respectively (entries 7 and 8). Although the use of *p*-methylbenzaldehyde gave a similar result, the use of *p*-methoxybenzaldehyde requires 96 h to obtain comparable yield (entries 9 and 11). This may be due to the relatively strong electron donating ability of the methoxy group that decelerates the reaction rate. The detailed mechanistic speculation is premature at this stage and work is underway to study this phenomenon in more detail.

The reaction of various aldehydes with  $\alpha$ -naphthyl acrylate **1g** was very fast as mentioned above. In addition to the conventional Baylis–Hillman products isolated, small quantities (3–10%) of cyclic acetates were identified dependent upon the substrates used. The minor product may come from the addition of the initial product with the unreacted aldehyde followed by elimination of  $\alpha$ -naphthol anion.<sup>5</sup> The cyclic acetal products are of great synthetic interest.<sup>7</sup> The preparation of various 1,3-dioxan-4-ones under several different reaction systems have been reported.<sup>3k,5,6</sup> In this study, the use of excess amounts of aldehydes (4.0 equiv.) under prolonged reaction time gave 1,3-dioxan-4-ones **4a–c** with good to high chemical yields (Scheme 1).

In summary, we have developed an efficient method for the synthesis of highly functionalized acrylates. Reaction of  $\alpha$ -naphthyl acrylate **1g** with both aliphatic and aromatic aldehydes

in the presence of DABCO (30 mol%) provided the corresponding  $\alpha$ -methylene  $\beta$ -hydroxy carbonyl derivatives with reasonable material yields within 20 min. *This represents, to the best of our knowledge, one of the best rate acceleration systems for wide ranges of aldehydes in Baylis–Hillman reactions under atmospheric pressure.* The pronounced acceleration of this reaction further extends the Baylis–Hillman reaction into a viable transformation. The asymmetric version of the Baylis–Hillman reaction using this reaction system is underway in our laboratory.

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## Notes and references

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