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Aqueous Baylis–Hillman reactions of cyclopent-2-enone using imidazole as catalyst

Sanzhong Luo,[a] Baolian Zhang,[a] Jiaqi He,[a] Adam Janczuk,[b] Peng G. Wang[b] and Jin-Pei Cheng[a,*]

[a]*Department of Chemistry, Nankai University, Tianjin 300071, China*
[b]*Department of Chemistry, Wayne State University, Detroit, MI 48202, USA*

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Abstract—In aqueous media, imidazole was found to catalyse Baylis–Hillman reactions of cyclopent-2-enone with various aldehydes to afford the desired adducts with high yields.

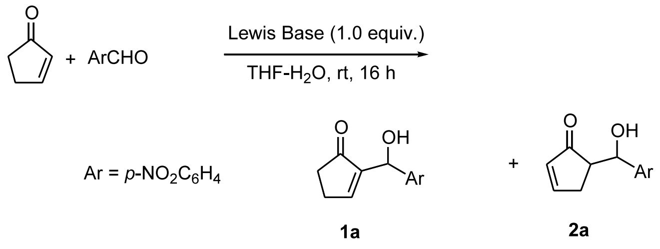
The Baylis–Hillman reaction, the coupling of activated alkenes with carbon electrophiles under the catalysis of tertiary amines, is emerging as a valuable carbon–carbon bond forming reaction.[1] The reaction has drawn increasing attention because it is selective (chemo-, regio-, diastereo-, enantio-), atom economical, and produces synthetically useful functionalised molecules under relatively mild conditions. The traditional Baylis–Hillman reaction involves nucleophilic and non-hindered tertiary amines like 1,4-diazabicyclo[2.2.2]octane (DABCO) as catalysts. However, the reaction typically suffers from sluggish reaction rates. To make the reaction more efficient, organic chemists have explored various other catalysts or catalytic systems such as DMAP,[2] chalcogenide/$TiCl_4$,[3] piperidine,[4] DBU,[5] pyrrolizidines,[6] and phosphines.[7] Recently, $TiCl_4$ was reported to catalyse the Baylis–Hillman reaction without the use of a Lewis base.[8] Herein, we disclose the use of imidazole as an efficient catalyst in the Baylis–Hillman reaction of cyclopent-2-enone in aqueous media.

The Baylis–Hillman reaction of cyclopent-2-enone or cyclohex-2-enone is sluggish under traditional conditions.[9] Various catalysts such as DMAP,[2] $TiCl_4$/chalcogenide,[3] and Bu_3P/phenols[10] have been explored but with limited success. Recent reports demonstrated that water could greatly accelerate the DABCO-catalysed Baylis–Hillman reaction of methyl acrylates, acrylonitriles, and even acrylamides.[11] These results prompted us to look at the aqueous Baylis–Hillman reaction involving cyclopent-2-enone. Unlike the reaction in organic solvent, DABCO was able to catalyse the reaction in aqueous media (Table 1, entry 1) to afford the Baylis–Hillman adduct **1a** and the aldol type product **2a** which was the major product (Scheme 1). The use of

Table 1. Lewis base effect in the Baylis–Hillman reactions of cyclopent-2-enone in aqueous media[a]

Entry	Lewis base	Time (h)	Yield (%)[b]	
			1a	**2a**
1	DABCO	36	32	56
2	DMAP	16	69	None
3	Et_3N	12	28	27
4	Me_3N/H_2O	12	25	29
5	Pyridine	4d	5[c]	None
6	Ph_3P	4d	No reaction	
7	Ph_3P/PhOH	4d	No reaction	
8	*N*-Methylimidazole	48	68[d]	None
9	Imidazole	16	92	None

[a] Mole ratio of aldehyde:cyclopent-2-enone = 1:1.5.
[b] Isolated yield.
[c] Over 90% of aldehyde was recovered.
[d] 15% of aldehyde was recovered.



Scheme 1.

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[*] Corresponding author. Fax: 86-10-68514074; e-mail: jpcheng@nankai.edu.cn

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Table 2. Solvent effects on the Baylis–Hillman reactions of *p*-nitrobenzaldehyde (1.0 mmol) and cyclopent-2-enone (1.5 mmol) in the presence of imidazole (1.0 mmol)

Entry	Solvent (v/v)	Time (h)	Yield (%)[a]
1	Dioxane	24	Trace[b]
2	Dioxane–H_2O (1/1)	24	73
3	CH_3CN	24	Trace[b]
4	CH_3CN–H_2O (1/1)	16	82
5	THF	30	27
6	THF–H_2O (1/1)	16	92
7	DMF	5d	No reaction
8	DMF–H_2O (1/1)	16	88
9	CH_3OH	30	65
10	CH_3OH–H_2O	20	82
11	H_2O	16	83

[a] Isolated yield.
[b] Over 90% of aldehyde was recovered.

triethylamine and trimethylamine gave similar results (Table 1, entries 3 and 4), with somewhat diminished yields. Among the other catalysts examined, triphenylphosphine or its combination with phenol did not exhibit any catalytic activity (Table 1, entries 6 and 7). DMAP appeared to be a promising catalyst in this reaction, resulting in the Baylis–Hillman adduct in 69% yield without any aldol product detected (Table 1, entry 2). Under aqueous conditions, even pyridine exhibited some catalytic effect, albeit much slower. It is interesting to note that imidazole and *N*-methylimidazole act as remarkable catalysts in aqueous media with the former giving the best results in terms of yield and reaction rate (Table 1, entries 8 and 9).

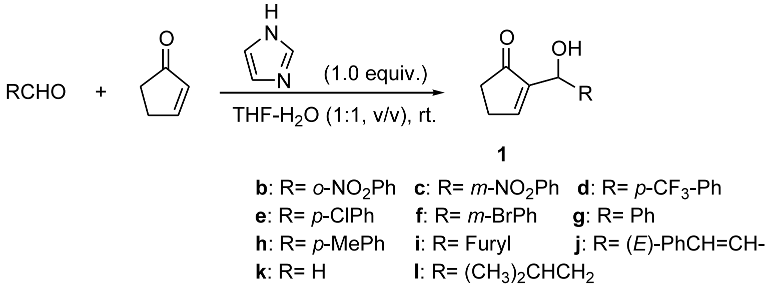
With imidazole as our optimal catalyst, we then systematically evaluated the solvent effect of this reaction using the reaction of *p*-nitrobenzaldehyde as a model (Table 2). Protic solvents proved to be crucial for the Baylis–Hillman reaction. Reactions in organic solvents proved to be slow (in dioxane, THF, or CH_3CN) or no reaction was observed at all (in DMF). The presence of water is essential for the success of the Baylis–Hillman reaction. Compared with the reactions in a pure organic solvent, both the yields and reaction rates in aqueous media were improved dramatically. For example, imidazole in DMF did not promote the reaction of *p*-nitrobenzaldehyde with cyclopent-2-enone, while in aqueous DMF (DMF:H_2O = 1:1, v/v), the desired Baylis–Hillman adduct was obtained in 88% yield after 16 hours. Alcohols were also evaluated, but were found to be less effective than water. The reaction carried out in pure methanol afforded the adduct **1a** in 65% yield after 30 hours (Table 2, entry 9). By conducting the reaction in aqueous methanol (MeOH:H_2O = 1:1, v/v), the yield of **1a** reached 82% in 20 hours (Table 2, entry 10). Even the reaction in pure water was effective, producing Baylis–Hillman adduct **1a** in 83% yield over 16 hours (Table 2, entry 11). Among the solvent systems examined in Table 2, we found that the binary medium consisting of THF and water was overall the solvent of choice.

We next investigated the scope and feasibility of the imidazole catalysed aqueous Baylis–Hillman reaction of cyclopent-2-enone with various aldehydes (Scheme 2, Table 3). For arylaldehydes bearing electron-withdrawing groups, the reaction took place smoothly to afford the desired Baylis–Hillman adducts in good to excellent yields (Table 3, entries 1–5). Similar results were obtained in the reaction of benzaldehyde, *trans*-cinnamaldehyde and heterocyclic aldehydes[12] such as 2-furaldehyde (Table 3, entries 6, 8 and 9). However, for

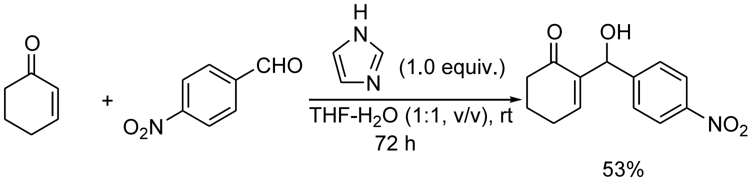
Table 3. Aqueous Baylis–Hillman reactions of aldehydes (1.0 equiv.) and cyclopent-2-enone (1.5 equiv.) in the presence of imidazole (1.0 equiv.)

Entry	R	Time (h)	Product	Yield (%)[a]
1	*o*-NO_2Ph	36	**1b**	69
2	*m*-NO_2Ph	40	**1c**	91
3	*p*-CF_3Ph	24	**1d**	84
4	*p*-ClPh	60	**1e**	88
5	*m*-BrPh	72	**1f**	75[b]
6	Ph	96	**1g**	74[c]
7	*p*-MePh	6d	**1h**	42[d]
8	Furyl	70	**1i**	84
9	(*E*)-PhCH=CH	72	**1j**	62[c]
10	H	72	**1k**	47[e]
11	$(CH_3)_2CHCH_2$	96	**1l**	27[c]

[a] Isolated yield.
[b] 20% of aldehyde recovered.
[c] 2.0 mmol of cyclopent-2-enone was used.
[d] 50% of aldehyde was recovered.
[e] 1 mmol cylopent-2-enone, 5 mmol formalin.



Scheme 2.



Scheme 3.

arylaldehydes bearing electron-donating groups such as *p*-tolualdehyde and aliphatic aldehydes, the reactions were slow (Table 3, entries 7, 10 and 11). One noteworthy point is that the imidazole catalysed aqueous Baylis–Hillman reaction is very clean, and in most cases, the unreacted aldehydes can be recovered quantitatively.

The typical procedure for the aqueous Baylis–Hillman reaction is as follows: At room temperature, a clear solution of the aldehyde (0.5 mmol), cyclopent-2-enone (0.75 mmol) and imidazole (0.5 mmol) in 1 ml of THF was charged with 1 ml of deionised water. The homogeneous reaction mixture was stirred at ambient temperature and monitored by TLC. Upon completion or after the indicated reaction time, the reaction mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give the desired products.

To the best of our knowledge, this is a new aqueous Baylis–Hillman reaction involving cyclopent-2-enone. As a weak Lewis base, imidazole alone has not been used as a Baylis–Hillman catalyst as yet. During the course of our work, Shi reported that using imidazole alone could not promote the Baylis–Hillman reaction of MVK in DMF, but could promote the reaction in combination with proline.[13] Our study shows that using aqueous media affects the reaction of cyclopent-2-enone dramatically, providing the desired Baylis–Hillman adduct **1** in moderate to high yields. Cyclopent-2-enone has been considered as being less reactive in the Baylis–Hillman reaction than MVK.[9,14] Besides cyclopent-2-enone, our reaction system was also applied to cyclohex-2-enone, the reaction at room temperature after 72 hours afforded the desired Baylis–Hillman adduct in moderate yield (Scheme 3).

In summary, we have disclosed a new Baylis–Hillman reaction system in aqueous media using stoichiometric imidazole as catalyst. Work to elucidate the reaction mechanism is under current attention. Efforts are also being made on further improvement of the reaction, in particular using a catalytic amount of imidazole, and also an asymmetric version of the reaction.

Acknowledgements

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