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Remarkable Rate Acceleration of Imidazole-Promoted Baylis−Hillman Reaction Involving Cyclic Enones in Basic Water Solution

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Abstract: The Baylis−Hillman reaction of cyclic enones was greatly accelerated in basic water solution with imidazoles as catalysts, which resulted in short reaction time, high yields, and expanding substrate scopes. Bicarbonate solution was shown to be the optimal reaction medium for the reaction in this study. The apparent "enhanced basicity" of imidazoles accounted for the rate increase in alkaline solution.

The Baylis−Hillman reaction, which involves the coupling of Michael acceptors with carbon electrophiles under the catalysis of a tertiary amine or phosphine, has drawn increasing attention during the past decades.[1] The resulting densely functionalized products allow numerous transformations and have versatile utilities in organic synthesis. To improve the applicability of Baylis−Hillman reactions, a variety of methods including physical as well as chemical attempts have been explored toward enhancement of reaction rate and extension of substrates scope.[2] Among these methods, the use of aqueous solution as reaction medium has been the recent research focus.[3] Hu and co-workers demonstrated that the Baylis−Hillman reaction of methyl acrylate and acrylamide could be accelerated simply by conducting the reaction in aqueous dioxane solution.[4] Most recently, Aggarval showed that the use of $Yb(OTf)_3$ could produce further acceleration in water or formamide.[5] In an earlier report, Augé examined the salt effect in aqueous Baylis−Hillman reaction.[3b] However, few reports have dealt with the effect of pH on the reaction.

β-Substituted enones have been considered less reactive in Baylis−Hillman reactions.[1a] The reaction of cyclic enones is sluggish or does not occur at all under traditional conditions. Various catalysts have been developed to promote the reaction of cyclic enones, and in some cases, good results were obtained.[6] In previous studies, we found that imidazole can catalyze the Baylis−Hillman reaction involving cyclic enones in aqueous THF solution.[7] In our continued efforts, we found that the reaction could be greatly accelerated by adjusting the pH value

TABLE 1. Imidazole (1a)-Catalyzed Reactions of Cyclopentenone with *p*-Nitrobenzaldehyde in Various H_2O Solutions[a]

entry	solution	pH	time (h)	yield[b] (%)
1	1 M Na_2CO_3	11.9	10 min	53[c]
2	satd $NaHCO_3$	8.9	40 min	72[c]
3	**1 M $NaHCO_3$**	**8.6**	**1.5**	**88**
4	1 M NaH_2PO_4−Na_2HPO_4	7.3	20	87
5	H_2O	7.0	1.5	48
6	1 M NaCl	7.0	12	90
7	1 M NaH_2PO_4−Na_2HPO_4	6.8	27	64 (88)[d]
8	1 M NaH_2PO_4−Na_2HPO_4	6.5	27	60 (92)[d]
9	1 M NaH_2PO_4−Na_2HPO_4	5.9	27	29 (91)[d]

[a] Reaction were carried out on a 0.5 mmol scale in 2 mL of water solution and 0.5 mL of THF, molar ratio of aldehyde/cyclopentenone/catalyst = 1.0:1.5:1.0. [b] Isolated yield based on aldehyde. [c] Decomposition of materials was observed. [d] Yield based on recovered aldehyde.

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SCHEME 1

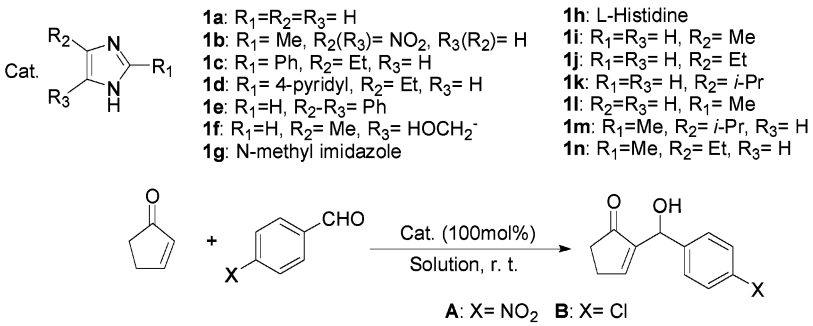


TABLE 2. Screening of Various Imidazoles in the Aqueous Baylis−Hillman Reaction Involving 2-cyclopentenone[a]

X = NO_2 (**A**)					X = Cl (**B**)				
entry	catalyst	medium	time (h)	yield[b] (%)	entry	catalyst	medium	time (h)	yield[b] (%)
1	**1b**	THF−H_2O	14	0	8	**1a**	THF−H_2O	40	74
		1M $NaHCO_3$	1.5	87			1 M $NaHCO_3$	11	90
2	**1c**	THF−H_2O	12	0	9	**1i**	THF−H_2O	24	86
		1 M $NaHCO_3$	22	46			1 M $NaHCO_3$	20	84
3	**1d**	THF−H_2O	12	0	10	**1j**	THF−H_2O	30	81
		1 M $NaHCO_3$	11	59			1 M $NaHCO_3$	20	87
4	benzoimidazole (**1e**)	THF−H_2O	48	30	11	**1k**	THF−H_2O	40	80
		1 M $NaHCO_3$	6	56			1 M $NaHCO_3$	20	82
5	**1f**	THF−H_2O	18	88	12	**1l**	THF−H_2O	24	85
		1 M $NaHCO_3$	4	89			1 M $NaHCO_3$	20	87
6	*N*-methyl imidazole **(1g)**	THF−H_2O	16	50	13	**1m**	THF−H_2O	26	86
		1 M $NaHCO_3$	12	60			1M $NaHCO_3$	10	88
7	L-histidine **(1h)**	THF−H_2O	40	39	14	**1n**	THF−H_2O	24	84
		1 M $NaHCO_3$	4	65			1 M $NaHCO_3$	10	86

[a] Reactions were carried out on a 0.5 mmol scale in 2 mL of THF−H_2O (v/v, 1/1) or 2 mL of 1 M $NaHCO_3$ and 0.5 mL of THF, molar ratio of aldehyde/cyclopentenone/catalyst = 1.0:1.5:1.0. [b] Isolated yield of pure products.

of the water solution. The screen process and the detailed results are presented herein.

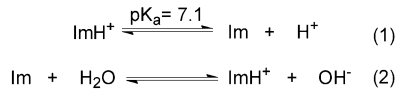
The reaction between cyclopent-2-enone and *p*-nitrobenzaldehyde in water was chosen as a model for screening purposes (Table 1). The reaction was conducted in 2 mL of water solution with 0.5 mL of THF added as cosolvent to solubilize the substrates.

In strong basic media (1 M Na_2CO_3 solution, pH = 11.9), the aldehyde was consumed within 10 min with the desired product isolated in only 53% yield (Table 1, entry 1). In addition, minor aldol product was also observed in the reaction. Reducing the basicity of the solution (pH 8.9−7.3) improved the reaction considerably (Table 1, entries 2−5). In a 1 M $NaHCO_3$ solution (pH = 8.6) cyclopent-2-enone reacted smoothly with *p*-nitrobenzaldehyde to afford the desired Baylis−Hillman adduct **1** in 88% yield after 1.5 h (Table 1, entry 3). As a comparison, the same reaction in aqueous THF gave 48% yield after 1.5 h (Table 1, entry 5). Performing the reaction in weakly acidic (pH 7.3−5.9) NaH_2PO_4−Na_2HPO_4 buffer system resulted in slow reactions (Table 1, entries 4 and 7−9). When applying the reaction in a NaCl solution, a slightly shorter reaction time was also observed (Table 1, entry 6). The above results clearly demonstrate that the Baylis−Hillman reaction of cyclopent-2-enone can be greatly accelerated in basic water solution. Among the conditions tested, the reaction in 1 M $NaHCO_3$ gives the best rate and yield. This was selected as our optimal condition in the following experiments.

Other imidazole derivatives have also been tested in the present condition (Scheme 1, Table 2). The same reaction in neutral aqueous THF was listed as comparison. As shown in Table 2, the EWG-substituted imidazoles (**1b**−**d**), which are inert in aqueous THF, were activated in aqueous sodium bicarbonate solution to promote the Baylis−Hillman reaction effectively (Table 2, entries 1−3). For example, in the presence of 2-methyl-4(3)-nitroimidazole (**1b**), the otherwise inert reaction in aqueous THF occurred smoothly in basic water solution to afford the desired Baylis−Hillman product with 87% yield in 1.5 h (Table 2, entry 1). For less reactive catalysts such as **1e**, **1f**, and **1g**, conducting the reaction in basic solution also produced obvious rate enhancement (Table 2, entries 4−6). It is noteworthy that the sluggish reaction catalyzed by L-histidine in aqueous THF was completed in 4 h in basic water solution affording the desired product with 65% yield. Unfortunately, no enantioselectivity was observed in this case (Table 2, entry 7). For the reaction catalyzed by only EDG-substituted imidazoles (**1i**−**1n**), the use of basic medium still produced rate enhancement but to a limited extent (Table 2, entries 9−14). In these cases, to make obvious comparison of the reaction rates, a less reactive aldehyde, *p*-chlorobenzaldehyde was employed for model studies. Among the catalysts tested, the bis alkyl-substituted imdazoles **1m** and **1n** together with imidazole itself gave the relatively better results in basic water solution in terms of reaction time and yields (Table 2, entrie 8, 13, and 14).

The rate increase in basic water solution may be rationalized by considering the interaction of imidazole with the medium, i.e., proton transfer between imidazole (pK_a = 7.1 in water) and its cation[8] (Scheme 2). As

SCHEME 2. Proton Transfer of Imidazole in Acidic Media (1) and Basic Media (2)



revealed in Scheme 2, in alkaline solution the proton exchange between water and imidazole is depressed, therefore leaving more neutral imidazole to take roles in Baylis-Hillman reaction as nucleophiles.[9] This was further supported by ^{15}N NMR analysis of [^{15}N] imidazole at various pH. Previously, Alei and co-workers reported that molar ration of ImH^+ decreased consecutively following the rising order of pH from 1.9 to 9.6. At pH above 9.6, neutral Im is the only existing species as determined by ^{15}N NMR analysis.[10] According to this observation, imidazole in strong basic solution (pH > 9.0) will demonstrate the best catalytic effect. However, in our reaction system, high pH (>9.0) may also lead to various side reactions due to the decomposition of cyclic enones under strong basic media, which in turn resulted in low output of the reaction. At this stage, it is clear that the increase of the effective molarity of neutral imidazole, the apparent "enhanced basicity", is most likely responsible for the further rate enhancement in alkaline solution.[11,12] For imidazole with low pK_a,[13] their protonated cations predominate at neutral pH. Consequently, neutralization of cations becomes prominent in basic pH and drastic change of activity will be observed as in the cases of **1b**−**f** (Table 2, entries 1−5). On the contrary, the nonprotonated form predominates for imidazoles with high pK_a at neutral pH, the consequent neutralization is less prominent in basic pH and limited rate enhancement were observed as in the cases of **1i**−**n** (Table 2, enties 9−14).

Having established the optimum conditions, we next explored the applicability of this acceleration strategy using imidazole (**1a**), 2-methyl-4-isopropylimidazole (**1m**), or 4-ethyl-2-methyl imidazole (**1n**) as catalysts (Scheme 3, Table 3). As shown in Table 3, in the presence of imidazole **1a** both the reaction rate and yields were improved considerably, comparing with the same reaction in distilled water (Table 3, entries 1, 3, 4, and 12). In aqueous THF (pH= 7), *p*-methylbenzaldehyde reacted with cyclopent-2-enone to give product **2E** in only 42% yield after 6 days, while the reaction in aqueous $NaHCO_3$ was improved to 87% output in 30 h. Notably, some highly unreactive aldehydes were successfully coupled with cyclopent-2-enone (Table 3, entries 6−11). For example, 2,4-dimethoxybenzaldehyde is a hindered and deactivated aldehyde but still gave moderate yields after 60 h (Table 3, entry 8). As an extremely deactivated aldehyde, dimethylamino benzaldehyde could also be applied in this condition with 13% yield after 36 h (Table 3, entry 10). The unreacted aldehydes could be recovered quantitatively. Aliphatic aldehydes such as isovaleraldehyde (Table 3, entry 12) worked well, but *n*-hexanal (Table 3, entry 13) afforded a low yield. In most cases, the reactions catalyzed by **1m** or **1n** gave comparable or even better results compared with the same reaction catalyzed by imidazole (Table 3, entries 2, 7, 9, and 11).

In addition to cyclopentenone, cyclohexenone was also successfully employed in this reaction system. Various aldehydes were attempted to produce the desired products with moderate to good yields (Scheme 4, Table 4). The acceleration effect was obvious in these cases. The reaction of *p*-nitrobenzaldehyde in aqueous THF gave 52% yield after 72 h; in contrast, the reaction in 1 M $NaHCO_3$ solution provided significantly higher yield and

SCHEME 3

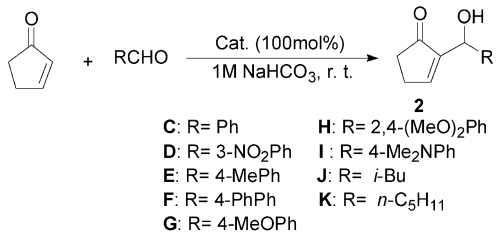
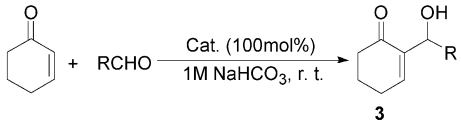


TABLE 3. Reactions of Cyclopentenone with Aldehydes in 1 M $NaHCO_3$ Solutions[a]

entry	aldehyde (R)	cat.	products	time (h)	yield[b] (%)
1	Ph	**1a**	**2C**	14 (96)[c]	83 (74)[c]
2	Ph	**1m**	**2C**	12	88
3	3-NO_2Ph	**1a**	**2D**	3.5 (40)[c]	92 (91)[c]
4	4-MePh	**1a**	**2E**	30 (6d)[c]	87 (42)[c]
5	4-PhPh	**1a**	**2F**	20	86
6	4-MeOPh	**1a**	**2G**	36	81
7	4-MeOPh	**1m**	**2G**	36	82
8	2,4-$(MeO)_2$Ph	**1a**	**2H**	60	36
9	2,4-$(MeO)_2$Ph	**1n**	**2H**	60	64
10	4-Me_2NPh	**1a**	**2I**	36	13
11	4-Me_2NPh	**1n**	**2I**	60	27
12	*i*-Bu	**1a**	**2J**	18 (96)[c]	75 (27)[c]
13	*n*-C_5H_{11}	**1a**	**2K**	24	29

[a] Reactions were carried out on a 0.5 mmol scale in 2 mL of 1 M $NaHCO_3$ and 0.5 mL of THF, molar ratio of aldehyde/enone/catalyst = 1.0:1.5:1.0. [b] Isolated yield based on aldehyde. [c] Numbers in parentheses refer to data of reactions in THF−H_2O (1/1, v/v).

SCHEME 4



(8) For similar proton transfer of imidazole in biological systems, see: (a) Silverman, D. N.; Lindskog, S. *Acc. Chem. Res.* **1988**, *21*, 30. (b) Lesburg, C. A.; Christianson, D. W. *J. Am. Chem. Soc.* **1995**, *117*, 6838.

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(11) In the absence of imidazole, only minor aldol product (ca. 5%) was detected in the reaction between 2-cyclopentenone and*p*-nitrobenzaldehyde in 1 M $NaHCO_3$ solution after 1.5 h. While in the presence of imidazole the Baylis−Hillman reaction predominated with trace aldol products detected.

(12) However, other factors such as salts effect (Table 1, entry 6) cannot be excluded presently, which may account, in part, for the rate acceleration, especially for the cases of imidazole with high pK_a like **1m** and **1n** (pK_a's around 8.3 by relating to 2, 4-dimethylimidazole, pK_a8.36). For salt effects in aqueous Baylis−Hillman reaction, see: Kumar, A.; Pawar, S. S. *Tetrahedron* **2003**, *59*, 5019.

(13) For pK_a values of imidazoles see: Schofield, K.; Grimmett, M. R.; Keene, B. R. T. *Heteroaromatic nitrogen compounds: the azoles*; Cambridge University Press: Cambridge, 1976; p 281.

TABLE 4. Reactions of Cyclohexenone with Aldehydes in 1 M $NaHCO_3$ Solutions[a]

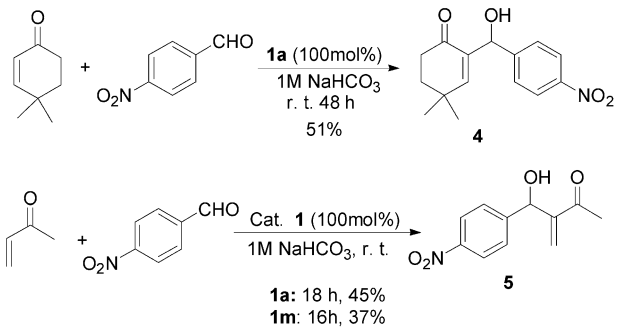
entry	R	cat.	products	time (h)	yield[b] (%)
1	Ph	**1a**	**3A**	90	45
2	Ph	**1n**	**3A**	72	38
3	4-ClPh	**1a**	**3B**	72	50
4	4-ClPh	**1n**	**3B**	72	50
5	4-NO_2Ph	**1a**	**3C**	8 (72)[c]	69 (52)[c]
6	3-NO_2Ph	**1a**	**3D**	12	68
7	2-NO_2Ph	**1a**	**3E**	30	51
8	H	**1a**	**3F**	15	65
9	*i*-Bu	**1a**	**3G**	24	32

[a] Reactions were carried out on a 1 mmol scale in 2 mL of 1 M $NaHCO_3$ and 0.5 mL of THF, molar ratio of aldehyde/enone/catalyst = 1.0:2.0:1.0. [b] Isolated yield based on aldehyde. [c] Numbers in parentheses refer to data of reactions in THF−H_2O (1/1, v/v).

shorter time (69% yield, 8 h). The use of alkyl-substituted imidazole **1n** gave comparable results (Table 4, entries 2 and 4). 4,4-Dimethyl-2-cyclohexenone was tried in the present conditions, the reaction with *p*-nitrobenzaldehyde was sluggish, producing the desired product **4** with 51% yield after 48 h. Under the optimal conditions, methyl vinyl ketone (MVK) was also attempted in the aqueous Baylis-Hillman reaction. The reaction between MVK and *p*-nitrobenzaldehyde afforded the desired product **6** with 45% yield after 18 h (Scheme 5).

In conclusion, we have developed favorable conditions for the Baylis−Hillman reaction involving cyclic enones. These improved conditions employed imidazoles as catalysts and sodium bicarbonate solution as reaction media. The reaction ran much faster in sodium bicarbonate solution than in distilled water, and showed obvious pH dependence. In basic water solution, the protonation of

SCHEME 5



imidazole is depressed, thus increasing the real active molarity of imidazole in catalysis. This apparent "enhanced basicity" most likely account for the further rate acceleration in basic aqueous media. Under the optimal conditions, the otherwise inert EWG-substituted imidazoles can be activated for effective catalysis. Finally, the conditions developed in this work were successfully applied to a variety of aldehydes and cyclic enones. Notably these conditions facilitate the efficient coupling of unreactive and hindered aldehydes.

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Supporting Information Available: General experimental procedure, spectra data, and ^1H NMR spectra for all adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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