Dramatic Rate Acceleration of the Baylis–Hillman Reaction in Homogeneous Medium in the Presence of Water
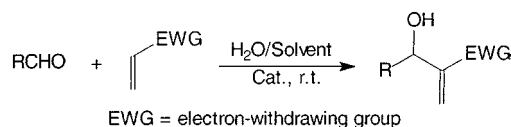
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ABSTRACT

EWG = electron-withdrawing group

In homogeneous H$_2$O/solvent medium, the reaction rate of aromatic aldehydes and acrylonitrile or acrylate was greatly accelerated, which led to shorter reaction time, lower reaction temperature, and higher yield. In this reaction, Me$_3$N, DMAP, DABCO, and urotropine were good catalysts. Except for low-carbon alcohols, tetrahydrofuran, 1,4-dioxane, and acetonitrile could be chosen as the solvent. Under this condition, the diastereoselective reaction of nitrobenzaldehyde and L-menthyl acrylate was realized with 88–99% de.

The Baylis−Hillman reaction was first reported in 1972.[1] This carbon−carbon bond-forming reaction can afford multifunctional adducts, which have been widely utilized in organic synthesis. Therefore, the Baylis−Hillman reaction has been drawing much attention from synthetic organic chemists in the past decade.[2] The major problem associated with this reaction is its slow reaction rate. In view of this situation, numerous methods, including chemical as well as physical attempts, have been made to accelerate the reaction with some good results.[3] Since 1994, several research groups reported that the Baylis−Hillman reaction could be accelerated in the presence of water. Bittman[4a] and Gaied[4b] have investigated the reaction of activated alkene and formaldehyde in the presence of water using DABCO (1,4-diazabicyclo[2,2,2]octane) and DMAP (4-(dimethylamino)-pyridine) as the catalyst, respectively. Lubineau[4c] has studied the rate acceleration effect of water on the DABCO-catalyzed coupling of benzaldehyde and acrylonitrile from the kinetic aspect. Most recently, Basaviah[4d] and Hu[4e] have investigated the trimethylamine- and DABCO-catalyzed Baylis−Hillman reaction in the presence of water. However, none of the aforementioned reports have dealt with the homogeneous medium in the presence of water.
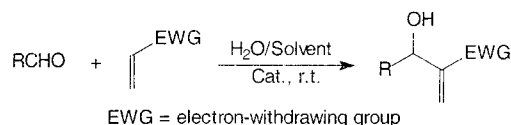
Recently, we found that an obvious rate acceleration was observed by the addition of low-carbon alcohols or other polar solvents, such as THF, 1,4-dioxane, acetonitrile, etc., to transform the heterogeneous mixture of aqueous trimethylamine and the substrate into a clear homogeneous

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Table 1. The Reaction of Aldehydes and Activated Alkene in Homogeneous H$_2$O/solvent medium at ambient temperature[a]

$$RCHO \ + \ \overset{EWG}{\underset{\parallel}{\|}} \ \xrightarrow[\text{Cat., r.t.}]{\text{H}_2\text{O/Solvent}} \ \overset{OH}{\underset{}{R}}\text{EWG}$$

EWG = electron-withdrawing group

entry	r	ewg	cat.	solvent	react. time (h)	product[b]	yield (%)[c]
1	4-O$_2$NC$_6$H$_4$	CN	Me$_3$N	MeOH	0.5	**1**[4d,5]	85
2	4-O$_2$NC$_6$H$_4$	CO$_2$Me	Me$_3$N	MeOH	2	**2**[4d,5]	86
3	4-O$_2$NC$_6$H$_4$	CO$_2$Et	Me$_3$N	EtOH	3.5	**3**[4d]	92
4	4-O$_2$NC$_6$H$_4$	CO$_2$Bu-n	Me$_3$N	n-BuOH	4	**4**[4d]	92
5	4-O$_2$NC$_6$H$_4$	CO$_2$Me	Me$_3$N	THF	2.5	**2**[4d]	99
6	4-O$_2$NC$_6$H$_4$	CO$_2$Me	Me$_3$N	1,4-dioxane	2.5	**2**[4d]	97
7	4-O$_2$NC$_6$H$_4$	CO$_2$Me	Me$_3$N	MeCN	3	**2**[4d]	88
8	4-O$_2$NC$_6$H$_4$	CO$_2$Me	DMAP	1,4-dioxane	4 (0 °C)	**2**[4d]	96
9	4-O$_2$NC$_6$H$_4$	CO$_2$Me	DABCO	1,4-dioxane	2.5	**2**[4d]	94
10	4-O$_2$NC$_6$H$_4$	CO$_2$Me	Urotropine	1,4-dioxane	96	**2**[4d]	87 (52% conversion)
11	4-NO$_2$C$_6$H$_4$	CO$_2$Me	Ph$_3$P	1,4-dioxane	36	**2**[4d]	58
12	4-NO$_2$C$_6$H$_4$	CO$_2$Men	Me$_3$N	1,4-dioxane	144	**5**	88 (83% de)[d]
13	3-NO$_2$C$_6$H$_4$	CO$_2$Men	Me$_3$N	1,4-dioxane	48	**6**	45 (99% de)[d]
14	2-furan	CO$_2$Me	Me$_3$N	MeOH	2.5	**7**[4d,6]	91
15	2-furan	CO$_2$Et	Me$_3$N	EtOH	4	**8**[4d]	96
16	2-furan	CO$_2$Bu^n	Me$_3$N	n-BuOH	24	**9**[4d]	94
17	C$_6$H$_5$	CN	Me$_3$N	MeOH	6	**10**[7]	92
18	C$_6$H$_5$	CO$_2$Me	Me$_3$N	MeOH	20	**11**[8]	88
19	4-ClC$_6$H$_4$	CN	Me$_3$N	MeOH	2.5	**12**	79
20	4-ClC$_6$H$_4$	CO$_2$Me	Me$_3$N	MeOH	8	**13**[4d]	77
21	4-FC$_6$H$_4$	CO$_2$Me	Me$_3$N	MeOH	60	**14**	87
22	2,4-Cl$_2$C$_6$H$_3$	CO$_2$Me	Me$_3$N	MeOH	6	**15**	85
23	4-CF$_3$C$_6$H$_4$	CO$_2$Me	Me$_3$N	MeOH	3	**16**	87
24	4-MeC$_6$H$_4$	CO$_2$Me	Me$_3$N	MeOH	168	**17**	92

[a] When 33% (w/v) aqueous trimethylamine was used as catalyst, all reactions of solid aldehydes were carried out on 2 mmol scale of the aldehyde, 6 mmol of activated alkene, and 2.5 mmol aqueous trimethylamine in 2 mL of solvent, all reactions of liquid aldehydes were carried out on 5 mmol scale of the aldehyde, 15 mmol of activated alkene, and 5 mmol of aqueous trimethylamine in 2 mL solvent. When other catalysts were used all reactions were carried out on a 1 mmol scale of the aldehyde, 3 mmol of activated alkene, and 0.5 mL of H$_2$O in 2 mL of solvent. [b] Structures of all the products, the known or unknown molecules, were confirmed by ^{1}H NMR and elemental analysis. [c] Isolated yield based on aldehydes. [d] De value was determined by HPLC with silica column (250 × 4.6, dp 5 μm), petroleum ether/2-propanol (95:5) as the eluent.

liquid. Hence, compared with the literature reported results, the addition product was obtained in less time and at low temperature with good to excellent yield (Table 1).

As shown in Table 1, in the aqueous trimethylamine homogeneous medium, the reaction of active aldehydes (such as 4-nitrobenzaldehyde) and acrylonitrile or acrylate has a fast reaction rate and high yield. Additionally, the reaction of nonactive aldehydes (such as benzaldehyde, fluoro-, chloro-, or methyl-substituted benzaldehydes, etc.) also has good results. On the other hand, in heterogeneous medium, the reaction of these nonactive aldehydes cannot provide good results because the reaction is extremely sluggish under this condition.[4d] Even the highly active 4-nitrobenzaldehyde and furaldehyde reacted with acrylate in heterogeneous medium can afford the product with only 56−59% and 30−35% yield, respectively, which was much lower than our

results of 86−92% (entries 2−4) and 91−96% (entries 14−16). Under the same conditions, the diastereoselective Baylis−Hillman reaction of 4- or 3-nitrobenzaldehyde and L-(−)-menthyl acrylate was realized with 83% and 99% de, respectively (entries 12 and 13).

When DMAP, DABCO, and urotropine were used as catalysts, the reaction of 4-nitrobenzaldehyde and methyl acrylate can be carried out with good results (entries 8−10) in the homogeneous H$_2$O/1,4-dioxane medium. Nevertheless, when triphenylphosphine was used as catalyst, the same reaction runs quite slowly with unsatisfactory results (entry 11).

Except for low-carbon alcohols, THF, 1,4-dioxane, and acetonitrile can also be used in the aqueous trimethylamine-catalyzed coupling of 4-nitrobenzaldehyde and methyl acrylate with satisfactory results.

In conclusion, the Baylis−Hillman reaction in H$_2$O/solvent homogeneous medium runs faster than that in heterogeneous medium in the presence of water. Furthermore, a better result (higher yield) was obtained. Under this condition, the diastereoselective Baylis−Hillman reaction was also realized

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with high de value. These results are helpful to the wider application of the Baylis−Hillman reaction in organic synthesis.