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Baylis–Hillman reactions in aqueous acidic media

Prakashanand Caumul and Helen C. Hailes*

Department of Chemistry, University College London, 20 Gordon Street, London WC1H OAJ, UK

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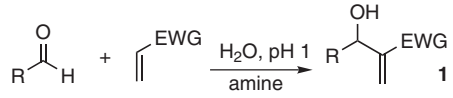
Abstract—The Baylis–Hillman reaction has been successfully performed under aqueous acidic conditions at pH 1, using a range of substrates and tertiary amines as catalysts.

Since the first report of the Baylis–Hillman reaction in the 1970s, this C–C bond forming reaction has been widely used in organic synthesis.[1] The reaction is typically catalysed by tertiary amine bases such as DABCO, DBU and quinuclidines.[1,2] More recently the reaction was reported to be accelerated in the presence of water. For example, aqueous formaldehyde was used for the hydroxymethylation of activated alkenes with DABCO or DMAP as catalysts, whilst Lubineau studied the rate acceleration effect of water on the DABCO-catalysed coupling between benzaldehyde and acrylonitrile.[3,4] The advantages of using binary aqueous solvent conditions have also been highlighted where high yields of Baylis–Hillman adducts were observed using DABCO and trimethylamine as bases.[5,6] Homogeneous aqueous solvent conditions, such as methanol and water have similarly been reported to lead to higher reaction yields.[7] It is now well established that the use of protic solvents accelerates the Baylis–Hillman reaction, and that the rate acceleration in water is dominated by hydrogen bonding, with a smaller contribution from hydrophobic effects.[8] A correlation between the basicity of the base and reactivity has also been established in solvents ranging from DMSO to methanol.[2] Recently, the mechanism of the Baylis–Hillman reaction has been re-evaluated, and the importance of proton transfer prior to amine elimination highlighted together with the consequences that this has on asymmetric catalysis.[9]

The use of Lewis acid conditions have also been reported for the Baylis–Hillman reaction including lanthanide triflates or lithium perchlorate with DABCO,[10,11] and $TiCl_4$ or Et_2AlI with no Lewis base,[12,13] in organic solvents. When $TiCl_4$ was used in the presence of a base the reaction was decelerated due to the formation of DABCO-Lewis acid complexes.[10] Conversely, a combination of $La(OTf)_3$ and co-ligand was found to enhance the reaction, which was attributed to carbonyl activation.[10] Although a variety of bases and Lewis acid conditions have successfully been used to carry out the Baylis–Hillman reaction, to our knowledge, the use of aqueous acidified conditions have not been reported. However, the use of such reaction conditions have been reported for the Diels–Alder reaction.[14,15] Herein, we report our preliminary investigations into the use of aqueous acidic conditions for the Baylis–Hillman reaction in the presence of tertiary amines.

Initial experiments were carried out using triethylamine, trimethylamine and DBU, which has been reported to be more effective than DABCO in water.[16] 2-Nitrobenzaldehyde and methyl acrylate were used as substrates and the reaction was performed at 0 °C. Immediately after the addition of substrates to the reaction the solution was adjusted to pH 1 with the dropwise addition of concd HCl. The use of Me_3N and DBU led to the isolation of the Baylis–Hillman adduct **1a** in 74% and 52% yields, respectively, although no product was observed when using Et_3N (Scheme 1, Table 1, entries 1–3). The pK_a of an amine's conjugate acid is a good measure of



Scheme 1. Baylis–Hillman reaction of aldehydes with EWG alkenes.

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* Corresponding author. Tel.: +44 (0)20 7679 4654; fax: +44 (0)20 7679 7463; e-mail: h.c.hailes@ucl.ac.uk

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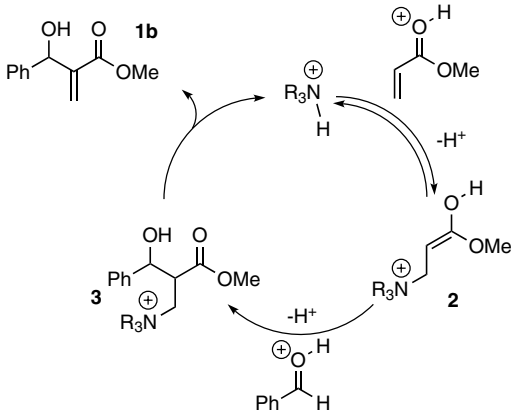
Table 1. Effect of pH and amine on the reaction shown in Scheme 1

Entry	Aldehyde (R)	Alkene (EWG)	Conditions[a]	Amine	Isolated yield (%)
1	2-$NO_2C_6H_4$	CO_2Me	pH 1, 0 °C	Me_3N	**1a**, 74
2	2-$NO_2C_6H_4$	CO_2Me	pH 1, 0 °C	DBU	**1a**, 52
3	2-$NO_2C_6H_4$	CO_2Me	pH 1, 0 °C	Et_3N	0
4	2-$NO_2C_6H_4$	CO_2Me	pH 1, 0 °C	**4**	**1a**, 54
5	2-$NO_2C_6H_4$	CO_2Me	pH 1, 0 °C	No amine	0
6	C_6H_5	CO_2Me	pH 6, 25 °C	**4**	**1b**, 26
7	C_6H_5	CO_2Me	pH 3, 25 °C	**4**	**1b**, 38
8	C_6H_5	CO_2Me	pH 1, 25 °C	**4**	**1b**, 41
9	C_6H_5	CO_2Me	pH 1, 0 °C	**4**	**1b**, 47
10	C_6H_5	CO_2Me	THF, 25 °C	DABCO	**1b**, 48
11	C_6H_5	CO_2Me	THF, 25 °C, 48 h	DBU	**1b**, 87
12[b]	C_6H_5	$CO_2C_5H_{11}$	pH 1, 25 °C	**4**	**1c**, 22
13[b]	C_6H_5	$CO_2C_5H_{11}$	pH 1, 0 °C	DBU	**1c**, 29
14[b]	2-$NO_2C_6H_4$	$CO_2C_5H_{11}$	pH 1, 0 °C	**4**	**1d**, 34
15[c]	C_6H_5	CN	pH 1, 0 °C	DBU	**1e**, 35
16[c]	C_6H_5	CN	pH 1, 0 °C	**4**	**1e**, 35

[a] General conditions (unless otherwise indicated): Aldehyde (1 mmol), acrylate (2.2 mmol), base (1 mmol), H_2O (20 ml) and adjusted to the pH indicated by the dropwise addition of concd HCl after the addition of all reaction substrates, 72 h. The product was extracted with EtOAc, dried, evaporated and purified.
[b] Reaction volume 10 ml.
[c] Reaction volume 2 ml.

the basicity of an amine, and the pK_as of trimethylamine, DBU and triethylamine are 9.8,[17] 11.3[2,18] and 10.6,[17] respectively. Thus, there was no apparent correlation between basicity and reaction outcome, suggesting that a combination of other factors such as steric effects, the stabilities of intermediates and a rate-limiting step may be important.

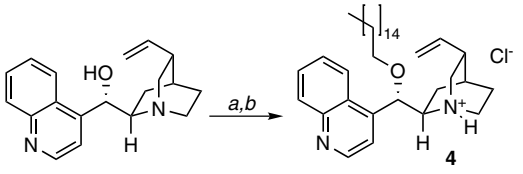
The catalytic cycle and intermediates will be different to that for the reaction under non-acidic conditions and is outlined in Scheme 2. The use of acidified media will lead to protonation of the acrylate and subsequent conjugate addition of the amine, presumably generated by deprotonation of the trialkylammonium ion in situ. The enol **2** then undergoes addition to the protonated aldehyde, and finally elimination of the amine group from **3** gives the adduct **1b**. At pH 1, protonation of the acrylate and aldehyde moieties will enhance the reaction and the intermediate **2** will be protonated rather than a zwitterionic species.



Scheme 2. Catalytic cycle of the Baylis–Hillman reaction under aqueous acidic conditions between benzaldehyde and methyl acrylate.

The Baylis–Hillman reaction was then investigated under further aqueous acidic conditions, but using a more sterically hindered amine that could influence the catalytic cycle during elimination of the amine from cationic intermediate **3**. The steric nature of the base has been suggested to contribute to a reduction in the reaction rate due to steric hindrance in intermediate **2**, resulting in a shift in the equilibrium back to the starting materials.[16] Indeed, previous reports have described the use of quinine-based alkaloids that could lead to enantiofacial stereodifferentiation in the Baylis–Hillman reaction: slow reactions or no products were observed.[19] However, more recently, cyclised conformationally rigid quinidines have been successfully used by Hatakeyama and co-workers in organic solvents.[20] The (+)-cinchonine analogue **4** was prepared via the *O*-alkylation of (+)-cinchonine under basic conditions and isolated as the hydrochloride salt. By derivatisation at the alcohol moiety, the surface active analogue **4** was formed, which had potential to enhance reactant aggregation properties and pre-orientation effects in water through micellar formation (Scheme 3).[14]

The Baylis–Hillman reaction was then carried out using 2-nitrobenzaldehyde, methyl acrylate and **4** in water adjusted to pH 1. The yield of **1a** isolated was similar to when using DBU, and comparable or significantly greater than previous reports using such non-cyclised cinchona alkaloids.[19,20] A control experiment in the



Scheme 3. Reagents and conditions: (a) NaH, DMF, $CH_3(CH_2)_{15}Br$, 50%; (b) HCl, dioxane, 88%.

presence of no amine resulted in the isolation of no product (Table 1, entry 5). The reaction was then performed using benzaldehyde over a pH range (at 0 or 25 °C) to confirm the effect of the acidity on the reaction. It was notable that the yield of the reaction increased with decreasing pH (Table 1, entries 6–9). The reaction was performed for comparative purposes in DBU and DABCO in THF. Although the yields and rate of reaction using **4** under aqueous acidic conditions were not as high as when DBU was used in organic solvents, it compared well with DABCO. Very small enantioselectivities (4–8% for the *R*-isomer) were observed when using compound **4** in the reaction.

Since the use of surface active salts such as **4** can help to solubilise substrates via the formation of aggregates, and pre-orientational effects can occur, pentyl acrylate was used as a substrate. The Baylis–Hillman product **1c** was isolated in 22% yield (Table 1, entry 12) and the addition of LiCl, a salting out agent, raised the yield under identical conditions to 34%: negligible enantioselectivities were observed in both cases. The use of DBU in water with pentyl acrylate at pH 1 gave **1c** in 29% yield, and the reaction using 2-nitrobenzaldehyde, pentyl acrylate and **4** was also performed to give **1d** in 34% yield (Table 1, entries 13 and 14). We concluded from the yield data that aggregation effects were not a dominating factor. The use of an alternative substrate, acrylonitrile with benzaldehyde and either salt **4** or DBU at pH 1 in water gave the adduct **1e** in 35% yield, the same yield in both reactions (Table 1, entries 15 and 16). Again when using **4** negligible enantioselectivities were observed. Overall, with several substrates, the use of DBU and catalyst **4** in acid water led to the formation of adducts in similar yields.

In summary, these preliminary results indicate that the use of aqueous acidic media leads to the isolation of Baylis–Hillman products with a range of substrates and tertiary amines. Under aqueous acidic conditions protonation and activation of the carbonyl moiety will occur, however the increase in activity is not as marked as with some Lewis acids reported.[10–13] This is most likely because deprotonation of the amine must occur prior to conjugate addition to the Michael acceptor. Nevertheless, this is the first reported example of a Baylis–Hillman reaction carried out under aqueous acidic conditions. This methodology has the potential to extend the use of the Baylis–Hillman reaction and reduce the need for performing reactions in organic solvents.

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