Baylis–Hillman reaction under solvent-free conditions — Remarkable rate acceleration and yield enhancement

Monmi Saikia and Jadab C. Sarma

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Abstract: A simple and efficient method has been developed for remarkable rate acceleration and yield enhancement of the Baylis–Hillman reaction under solvent-free "neat conditions" and solvent-less isolation of products. Reaction of equimolar quantities of aldehyde and olefin in the presence of 20 mol% of DABCO under neat conditions affords the highest yield in most cases within the shortest reaction time, giving support to the mechanisms of proton transfer in protic and aprotic solvents. Solvent-free conditions are found to be especially fast, selective, and high yielding for aromatic aldehydes.

Key words: Baylis–Hillman reaction, solvent free, rate acceleration, catalyst.

Résumé : On a mis au point une méthode simple et efficace augmenter d'une façon remarquable la vitesse et le rendement de la réaction de Baylis–Hillman, dans des conditions sans solvant tant pour la réaction que pour l'extraction des produits. Dans la plupart des cas, les meilleurs rendements ont été obtenus avec les temps de réaction les plus courts par la réaction de quantités équimolaires d'aldéhyde et d'oléfine en présence de 20 mol % de DABCO dans des conditions sans solvant; ces résultats apportent un support au mécanisme de transferts de proton dans des solvants protiques et aprotiques. On a trouvé que pour les aldéhydes aromatiques, les conditions sans solvant sont particulièrement rapides, sélectives et qu'elles donnent des rendements élevés.

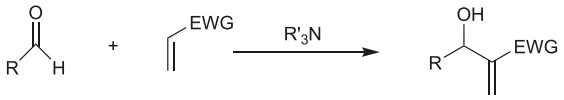
Mots-clés : réaction de Baylis–Hillman, sans solvant, accélération de la vitesse, catalyseur.

Introduction

The Baylis–Hillman reaction[1–4] is an important reaction for carbon–carbon bond formation involving a tertiary amine (or phosphine) catalyzed coupling of an aldehyde with an α,β unsaturated system. This reaction affords a highly functionalized product known as the Baylis–Hillman adduct, with a scope for various chemical manipulations to create frameworks for complex molecules (Scheme 1). Although the reaction was first reported in the early 1980s,[5] its synthetic appreciation was at a low profile in the initial stages. For the last two decades, the Baylis–Hillman reaction has attracted the curiosity of synthetic organic chemists, and the reaction has followed an exponential growth in terms of all the three essential components, i.e., activated olefin, the electrophile, and the catalyst.

Usually the Baylis–Hillman reaction is a slow reaction and requires a few days to a few weeks for completion depending upon the reactivities of both the activated alkene and the aldehyde.[1] Becase of the synthetic potential[6] of the Baylis–Hillman adducts, various modifications of the experimental protocol have been proposed. Several groups of scientists had been directing their efforts to solve the problem of slow reaction rate vis-à-vis enhancement of the chemical yield. In this connection some groups of workers have

Scheme 1.



studied the variations of reaction speed and chemical yield by using different Lewis bases such as DABCO, DMAP, DBU, Ph_3P, imidazole, ionic liquid immobilized quinuclidine, tetramethyl guanidine, etc.[7] A few others have tried different solvents or solvent mixtures along with the effect of stoichiometry of the reactants and the catalyst.[8] Additives such as salt, another base as co-catalyst,[9] or external influences such as high pressure,[10] mechanical agitation,[11] ultrasound agitation,[12] etc., were applied to try to improve the rate as well as the yield of the reaction.

Coelho et al.[12] reported on the application of ultrasound radiation in the Baylis–Hillman reaction to obtain augmentation of the reaction rate and the chemical yield. They compared the reactivity of two catalysts viz. tri-*n*-butyl phosphene and 1,4-diazabicyclo[2.2.2]octane (DABCO) and found the later to be the catalyst of choice under ultrasound irradiation. The time for completion of the reaction was drastically reduced from 72 to 16 h for 4-nitrobenzaldehyde and from 480 to 96 h for piperonal and so on. Not only was

Received 7 December 2009. Accepted 25 August 2010. Published on the NRC Research Press Web site at canjchem.nrc.ca on 1 December 2010.

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the reaction rate enhanced, but also the chemical yield was improved substantially.

Another report of rate acceleration for the Baylis–Hillman reaction was published by Park et al.[13] They found remarkable rate acceleration by using octanol as an additive to the Baylis–Hillman reaction mixture.

Very recently deSouza et al.[14] reported rate and yield enhancement of the Baylis–Hillman reaction through utilization of an aqueous – organic solvent mixture. For the coupling of 4-nitrobenzaldehyde with acrylonitrile, *tert*-butyl alcohol – water (60:40) was reported to be the system of choice (reaction time, 20 min; yield, 99%), whereas for the same aldehyde with methyl acrylate, DMSO–water (60:40) gave better results (reaction time, 150 min; yield, 90%). In both cases, a fast reaction was observed only when the catalyst was used in a stoichiometric amount. Earlier, Yu et al.[8] developed a similar set of conditions using a stoichiometric amount of base catalyst DABCO and an aqueous medium to overcome the problem of long reaction time. To cite an example, the reaction of 4-nitrobenzaldehyde with methyl acrylate in the presence of DABCO (1:3:1 ratio) yielded 83% of the adduct in 3 h.

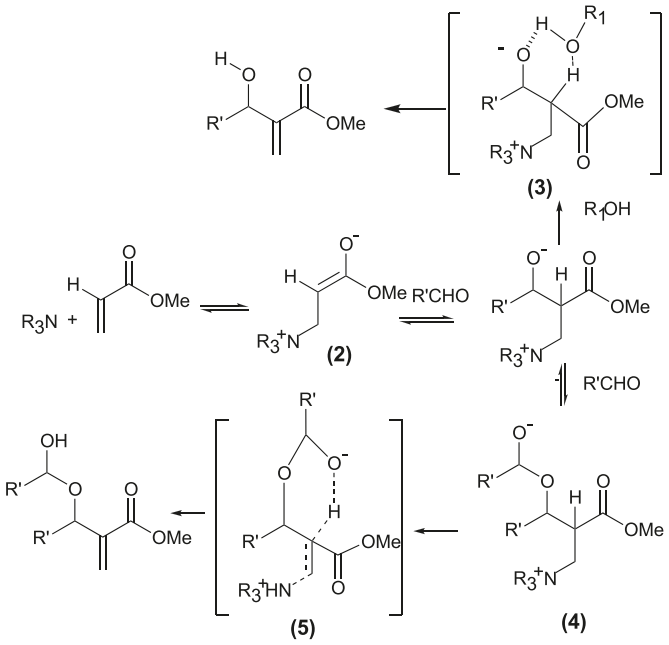
Porto et al.[15] and Rosa et al.[16] have used an ionic solvent for better yield and a faster reaction rate. Reaction time was also reduced notably and the yield of the adduct increased substantially as in the case of the reaction of 4-nitrobenzaldehyde with methyl acrylate, which afforded a 99% yield in 4 h.

Results and discussion

The Baylis–Hillman reaction itself falls under the green chemistry transformation because of its total atom efficiency. Under green chemistry protocol, a solvent-free non-stoichiometric catalytic reaction with atom efficiency is a major criterion of greenness. Although a lot of reports have dealt with the issue of rate and yield enhancement for the Baylis–Hillman reaction, there has been no reporting from the green chemistry point of view, especially with regards to the reaction under neat conditions for synthetic utilization. However, a mechanistic study by Aggarwal et al.[17] used neat conditions. In other reports of the reaction under solvent-free neat conditions by Aggarwal and Mereu,[18], Park et al.[13], and Mack and Shumba[11], an additional co-catalyst or some external device is being used along with DABCO, and the thrust of the study revolves round the co-catalyst or the external device to show its importance in rate and yield enhancement. Mack and Shumba[11] stressed the utility of a high-speed ball milling device as a novel technique for better yield of the reaction products in as little as 0.5 h of reaction time. Whereas in the study by Park et al.[13] octanol was used as the additive for the acceleration of rate and enhancement of yield, Aggarwal and Mereu[17] demonstrated that lanthanoids were an essential co-catalyst.

In a recent report, Das et al.[19] demonstrated a practical method for the *aza*-Morita–Baylis–Hillman reaction using α-amido sulfone as the substrate. Here, an excess of alkene was used under neat conditions with a stoichiometric amount of catalyst. Gajda and Gajda[20] also reported an *aza*-Morita–Baylis–Hillman reaction with *N*-carbamate protected α-amidoalkyl-*p*-tolylsulfones using excess alkene. Similar in situ generation of imines in the *aza*-Morita–Baylis–Hillman reaction was also reported recently by Abermil et al.[21] and Cihalova et al.[22] They used chlorinated compounds such as CH_2Cl_2 and $CHCl_3$ as the solvent of choice.

Scheme 2.



From the scrutiny of the reactions reported by Park et al.,[13] a kinetic study done by McQuade and co-workers,[23] a re-evaluation of the mechanism done by Aggarwal and Lloyd-Jones[24], and a computational study done by Aggarwal and Harvey[25], it becomes apparent that proton transfer is accelerated in the presence of a protic additive such as alcohol. (Scheme 2) Aggarwal and Harvery[25] has again shown that in the absence of a protic additive, the reaction is autocatalytic, because the product alcohol itself can act as a hydrogen-bond donor to promote the proton transfer in the transition state (TS) (**3**).[17] In aprotic solvent or under neat conditions without sufficient quantities of alcohol at the early stage of the reaction, McQuade's[23] pathway involving the hemiacetal intermediate (**5**) must be operating. In time, as the reaction progresses (>20% conversion) the reaction becomes autocatalytic. Protonation of the enolate (**2**) by octanol as the solvent (not as an additive) may be the reason for the slow reaction as reported by Park et al.[13] Indeed this more favorable interaction would stabilize the enolate and render it less reactive and thus slow down the reaction rate.

Considering all these factors we decided to try the Baylis–Hillman reaction under solvent-free conditions, keeping the other parameters constant. To our satisfaction the reaction carried out under neat conditions gave a far better result than the ones done with additives like octanol, lanthanoides, etc. In all cases the reaction was over within a very short time, giving a higher yield than those reported in all the other methods. Our observations are compiled in Table 1. The reactions used an equimolar concentration with 20% of DABCO as the catalyst.

For direct comparison of the results obtained using the octanol additive method, we performed a few reactions of aldehydes with methyl vinyl ketone under neat conditions,

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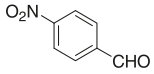
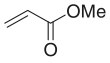
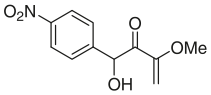
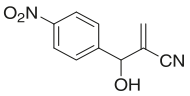
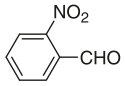
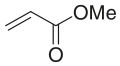
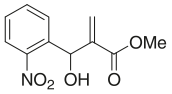
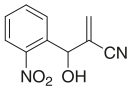
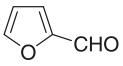
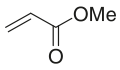
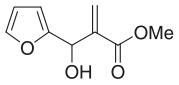
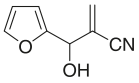
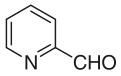
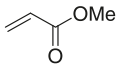
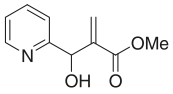
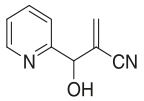
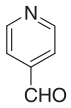
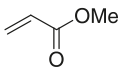
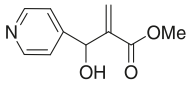
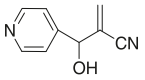
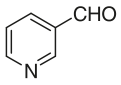
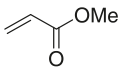
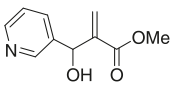
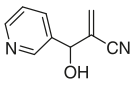
Table 1. Baylis–Hillman reaction of aldehyde with Michael acceptor.

Entry	Aldehyde	Alkene	Time (h)	Product[a]	Yield (%)	Ref.
1			0.30		99	12
			0.20		97	7
2			0.75		98	7
			0.20		99	–
3			0.75		97	12
			0.30		99	–
4			0.75		98	12
			0.20		98	12
5			0.5		100	7
			0.30		99	–
6			0.75		100	12
			0.20		99	–

keeping the other parameters fixed. The comparative results are shown in Table 2. In all the cases, except for acetaldehyde, the present method gives a better yield in a shorter time period. For aliphatic aldehydes such as propanal and its higher homologues, the reaction is very slow as usual. In fact, decanal remained unchanged for 15 days under neat conditions. For formaldehyde and acetaldehyde, there was some reaction with the formation of a BH adduct and the dimer at a reasonable speed. As these aldehydes were used as a water solution, and considering the rate enhancement of the small aliphatic aldehydes to be due to the presence of water (a hydrogen-bond donor), we tried the reaction of propanal and decanal by adding three drops each of water in the medium, respectively. In both the cases with methyl acrylate and methyl vinyl ketone as the reactive alkenes, there was no appreciable change over 24 h, thereby indicat-

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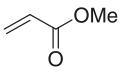
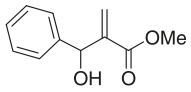
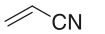
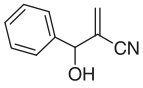
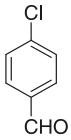
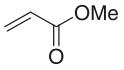
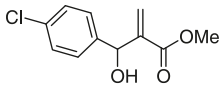
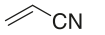
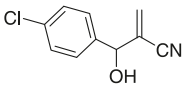
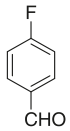
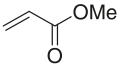
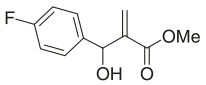
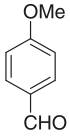
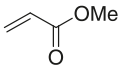
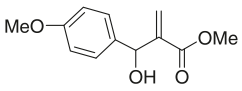
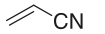
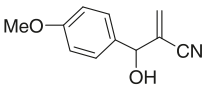
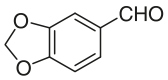
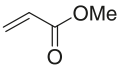
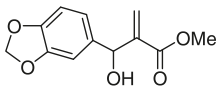
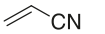
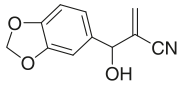
Table 1. (*concluded*).

Entry	Aldehyde	Alkene	Time (h)	Product [a]	Yield (%)	Ref.
7			1.5		94	12
			1.0		99	7
8			4.5		98	12
			1.2		99	7
9			3.5		100	8
10			45		75	12
			16		98	7
11			42		80	12
			15		95	12

Note: Aldehyde (1 mmol) was stirred with alkene (1mmol) in presence of DABCO (20 mol%) at room temperature.
[a] Products were characterized by using ^{1}H and ^{13}C NMR, FT-IR, and MS analysis.

ing the present method to be selective for aromatic aldehydes.

In many earlier reactions, alkene was added in large excess with 100% catalyst loading. Later on, the stoichiometry was brought to equimolar with 50% to 15% loading of the catalyst. If participation of the aldehyde as a hemiacetal in the TS for proton transfer is important in aprotic solvents, then an excess of aldehyde should enhance the rate of the reaction. Therefore, we used a few otherwise sluggish aldehydes by adding 10% excess to that of the alkene under neat conditions with 20% of catalyst (DABCO) loading to see the difference. From the results shown in Table 3, it is clear that for the substrates of entries 1–3 the reaction time was reduced substantially (in comparison with Table 1). For 4-methoxy benzaldehyde, the yield was enhanced, but the reation time remained the same, and for piperonal, there was no appreciable change.

In reactions generally carried out under solvent-free conditions, the solvent is normally required to be used at a later stage (at the time of extraction of the product from the reaction mixture) and, therefore, the claim for a solvent-free green method substantially gets diluted. We, therefore, tried a representative reaction of 4-nitrobenzaldehyde with methyl acrylate in a 2 g scale and worked up by pouring the reaction mixture into ice-cold water. Precipitated product was recrystallized from ethanol to get 98% yield of the pure

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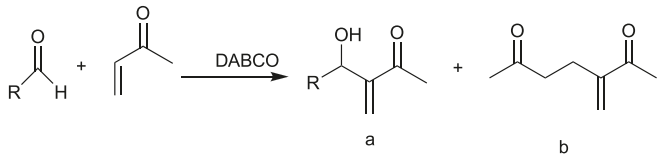
Table 2. Comparative results of the two methods.



				Yield (%)		
Entry	R	Alkene	Time (h)	a	b	Methods
1	4-$NO_2C_6H_4$	MVK	1	94	2	Present study
			12	70	0	Reference 13
2	4-ClC_6H_4	MVK	6	90	3.5	Present study
			12	70	0	Reference 13
3	4-$MeOC_6H_4$	MVK	50	68	10	Present study
			12	18	43	Referenec 13
4	Furfuryl	MVK	0.5	95	0	Present study
			12	26	10	Reference 13
5	CH_3	MVK	3	78	10	Present study
			12	90	6	Reference 13

Note: MVK, methyl vinyl ketone.

Table 3. The effect of excess aldehyde.

Entry	R	EWG	Time (h)	Yield (%)
1	4-ClC_6H_4	COOMe	3.5	98
2	4-$NO_2C_6H_4$	COOMe	0.25	99
3	2-$NO_2C_6H_4$	COOMe	0.5	99
4	4-$MeOC_6H_4$	COOMe	45	80
5	Piperonal	COOMe	42	80

Note: EWG, electron-withdrawing group.

crystalline product. Thus, the method turned out to be a complete solvent-free green method.

Conclusion

In conclusion, we report a green method with significant rate enhancement as well as yield improvement of the Baylis–Hillman reaction through solvent-free conditions. The method is bestowed with several unique green features such as a solvent-free neat reaction, a catalytic transformation, a solvent-less simple work up procedure for large-scale reaction, a higher yield than those reported so far in almost all cases, and the shortest reaction time. Hence, it significantly contributes to synthetic organic chemistry.

Experimental

General procedure for the Baylis–Hillman reaction

In a 50 mL round bottom flask, an equimolar quantity of aldehyde was stirred with an electron-deficient alkene with 20 mol% of DABCO as the catalyst at room temperature. The progress of the reaction was monitored by TLC. On completion, the reaction was poured into water and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to get a solid mass, which in most cases was recrystallized from ethanol. Otherwise, filtering through a short silica gel column yielded the pure product.

When the reaction was carried out in a 2 g scale of 4-nitrobenzaldehyde, the product was isolated by pouring the reaction mixture over ice-cold water followed by filtering and recrystallization of the product from ethanol. All the known compounds reported in Table 3 have been found to give spectral data identical to those reported. The spectral and other data of the compounds not reported earlier are reproduced here.

3-Hydroxy-2-methylene-3-(2-nitrophenyl) propanenitrile (entry 2, Table 3)

Gummy mater. IR ($CHCl_3$, cm^{-1}): 3436, 3090, 2229, 1527, 1348, 1055, 1038, 957. ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.06 (m, 1H), 7.85 (m, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 6.18 (s, 1H), 6.15 (s, 1H), 5.98 (s, 1H), 3.42 (brs 1H). ^{13}C NMR: 147.90, 134.58, 134.30, 132.24, 129.80, 129.16, 125.16, 124.17, 116.62, 69.14. MS (*m*/*z*): 204 (M^+, 2), 202.8 (16), 186.7 (100), 170.9 (6), 158.7 (22), 140.5 (64), 113.9 (8).

3-Hydroxy-2-methylene-3-(2-furyl) propanenitrile (entry 3, Table 3)

Gummy mater. IR ($CHCl_3$, cm^{-1}): 3420, 2919, 2231, 1625, 1399, 1145, 1014, 958. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.44 (s, 1H), 6.41 (m, 2H), 6.20 (s, 1H), 6.15 (s, 1H), 5.36 (s, 1H), 2.43 (brs, 1H). ^{13}C NMR: 151.45, 143.42, 131.43, 123.28, 116.70, 110.75, 108.77, 67.70. MS (*m*/*z*): 150 (M + 1, 6), 148.9 (60), 131.8 (10), 120.9 (5), 97.2 (50), 96.7 (100), 76.9 (12), 68.9 (22).

3-Hydroxy-2-methylene-3-(4-pyridyl)propanenitrile *(entry 5, Table 3)*

mp 111–113 °C (ethanol). IR ($CHCl_3$, cm^{-1}): 3427, 2854, 2227, 1603, 1414, 1072, 1060, 1005. ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.57 (m, 2H), 7.38 (m, 2H), 6,19 (s, 1H), 6.11 (s, 1H), 5.35 (s, 1H). ^{13}C NMR: 149.55, 149.42, 130.84, 125.72, 121.65, 116.56, 72.57. MS (*m*/*z*): 161 (M + 1, 14), 159.9 (66), 131 (8), 107.8 (100), 105.9 (8), 79.9 (38), 77.9

(24), 52 (74). Anal. calcd. for $C_9H_8N_2O$: C 67.49, H 5.03, N 17.48; found: C 67.15, H 5.07, N 17.21.

3-Hydroxy-2-methylene-3-(3-pyridyl)propanenitrile (entry 6, Table 3)

mp 101–103 °C (ethanol). IR ($CHCl_3$, cm^{-1}): 3420, 2850, 2227, 1597, 1582, 1480, 1428, 1067, 1030, 955. ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.43–8.45 (overlapping m, 2H), 7.81 (d, J = 7.8 Hz, 1H), 7.34–7.38 (m, 1H), 6,19 (s, 1H), 6.08 (s, 1H), 5.36 (s, 1H). ^{13}C NMR: 148.9, 147.4, 136.3, 135.2, 130.5, 126, 124.2, 116.8, 71.6. MS (*m/z*): 161 (M + 1, 16), 160 (M + 50), 141.9 (6), 130.8 (8), 107.9 (100), 79.9 (58), 77.9 (26), 52.9 (10). Anal. calcd. for $C_9H_8N_2O$: C 67.49, H 5.03, N 17.48; found: C 66.97, H 5.06, N 17.14.

Acknowledgements

The authors are grateful to the Director, North-East Institute of Science and Technology (NEIST), Jorhat, India, for providing the facilities and to Dr. N.C. Barua for his interest and encouragement during the work. Thanks are also due to the Analytical Chemistry Division for recording the spectra. The authors would also like to thank one of the reviewers for his suggestions and specific comments, which helped in revising the manuscript.

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