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Et_3N/H_2O: A green and inexpensive organocatalytic medium for efficient Baylis-Hillman reaction

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ABSTRACT

A new organocatalyzed method is developed for Baylis–Hillman reactions of cyclohex-2-enone with various aromatic aldehydes in the presence of water and catalytic quantities of triethylamine. All reactions take place at room temperature and relatively good yields of various products are obtained within a time frame which does not exceed 24 hours. The mild reaction conditions used in the present method and the versatility of the process are the main advantages of this procedure. As a result, products of the Baylis–Hillman reaction of cyclohex-2-enone with various aromatic aldehydes bearing electron withdrawing and electron releasing groups are obtained under inexpensive organocatalytic conditions.

***Keywords**: Baylis–Hillman reaction, Organocatalyst, Aqueous conditions, Room temperature.*

1. Introduction

The use of organocatalysts [1-3] and aqueous conditions [4-7] in today's synthesis are two rapidly growing fronts of "green chemistry". On one hand, organocatalysts cause acceleration of reactions by using substoichiometric amounts of an organic additive which contains no metal in its composition.

On the other hand, unexpected rate and selectivity enhancement in various organic transformations is achieved by the use of water, the most abundant chemical on our planet and a medium that its use has been rejected for many years by synthetic chemists.

The Baylis–Hillman (BH) reaction, which was discovered in the early 1970's [8-9], has been one of the most practiced reactions in synthetic organic chemistry since then. This popularity is due to the ability of the reaction that can accommodate several functional groups in a fairly small region of the final product. In addition, the BH reaction requires simple starting materials and is an atom-economic one-pot process [10]. An interesting feature of the reaction is that the BH adducts can be themselves used as intermediates for the synthesis of natural products [11], bioactive molecules [12], and various heterocyclic [13] and homocyclic compounds [14].

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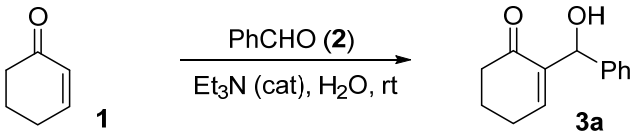
The reaction, however, suffers from two major limitations. The first is the inherent low reactivity of some of the starting enones. This has been tried to be suppressed by developing new strategies involving the use of elevated pressure [15], microwave heating [16], ultrasonic irradiation [17], heterogeneous catalysts [18], ionic liquid media [19], Lewis acids [20], and organocatalysts [21] or by using other nucleophiles rather than amines [22]. Several reports also exist on the employment of aqueous media for enhancement of the BH reaction scopes [23]. The second limitation arises when substrates with acidic α hydrogens are subjected to BH reaction, where parallel competition of aldol reaction/condensation may be observed [24].

In the framework of our studies on developing environmentally benign synthetic procedures [25-27] and in continuation of our investigations on organocatalyzed BH reactions [28], we would like here to report a full account on the use of inexpensive triethylamine/water (Et_3N/H_2O) conditions for BH reactions of cyclohex-2-enone 1 (Scheme 1). Although the BH reaction usually leads to better results for aldehydes bearing electron withdrawing groups [10,28], in the present work several aldehydes with various electronic natures have successfully reacted with the enone to yield the corresponding BH adducts.



Scheme 1. Typical BH reaction of **1** with benzaldehyde.

2. Experimental

2.1. General

Melting points were determined with a Buchi melting point apparatus and are uncorrected. NMR spectra are obtained on a FT-NMR Bruker Ultra Shield^{TM} (500 MHz) as $CDCl_3$ solutions using TMS as internal standard reference. Elemental analyses are performed using a Thermo Finnigan Flash EA 1112 instrument. MS spectra are obtained on a Fisons 8000 Trio instrument at ionization potential of 70 eV. TLC experiments are carried out on pre-coated silica gel plates using petroleum ether/EtOAc (5:1) as the eluent. All other chemicals are commercially available. Aldehydes are redistilled or recrystallized prior to being used. All products were characterized by obtaining their physical and spectral data.

2.2. General procedure

To a stirred mixture of an aldehyde (3.0 mmol) and cyclohex-2-enone 1 (3.0 mmol) in water (2 ml), was added Et_3N (20 mol%). The reaction mixture was stirred at ambient temperature for the time specified in the Table 2. After TLC monitoring (EtOAc/petroleum ether, 1:2 as the eluent) showed completion of the reaction, dilute HCl was added to the reaction mixture and the mixture was extracted with ether (3 × 5 mL). The Et_2O phase was rinsed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was fractionated by column chromatography using EtOAc/petroleum ether (1:2) as the eluent.

3. Results and Discussion

In order to assign the best conditions, the model reaction between benzaldehyde and cyclohex-2-enone 1 (Scheme 1) was studied under different conditions, as the results are summarized in the Table 1. The best conditions were obtained when an equimolar mixture of the two reactants was treated in water with 20 mol% Et_3N leading to 81% formation of 3a after 24 h (entry 1). When either the organocatalyst (entry 2) or water (entry 3) was omitted, the reaction rate reduced considerably. The same reactions in the presence of other amines gave 3a, but in lower amounts (entries 4-7).

The optimized conditions (Et_3N (20 mol%)/H_2O) were then used to examine the generality of the reaction (Table 2). In addition to benzaldehyde (entry 1), electron donating (entry 2) and electron withdrawing substituted derivatives of 2 (entries 3-6) also reacted equally well to produce high yields of 3b-f within 15-24 h. The conditions were also amenable for the same reactions with homocyclic (entries 7-8) and heterocyclic (entries 9-10) aromatic aldehydes. This was the case also for aliphatic aldehydes (entries 11-13) to give their respective BH adducts, although these reactants are usually prone to undergo undesired side reactions due to having active α hydrogens.

Table 1. Optimization of the conditions for BH reaction of **1** with benzaldehydes.

Entry	Conditions[a]	Yield (%)[b,c]
1	Et_3N /H_2O	81
2	H_2O	10
3	Et_3N	0
4	DBU/H_2O	52
5	DABCO/H_2O	50
6	DMAP/H_2O	46
7	Imidazole/H_2O	40

[a]20 Mol% of amines are used.
[b]Isolated yield.
[c]All reaction times are 24 h.

Based on these observations, a mechanism can be suggested for the reaction, as depicted in the Scheme 2. The enone substrate can bound to H_2O molecules through hydrogen bonding to get better attacked by the amine organocatalyst and produce a Michael adduct intermediate. This intermediate can then add to the aldehyde to produce the final BH adduct after an elimination step and reproduction of Et_3N. This help the reaction proceed catalytically by recovering the amine molecule. Hydrogen bonded activation of organic reactants, which justifies the role of water in this reaction, has precedence and observed by others as well before [35].

4. Conclusions

In summary, a new method is developed for BH reactions under organocatalytic conditions. Reactions reach to completion in short time periods, the catalyst and the medium are inexpensive and environmentally safe to be used, and yields of single products are obtained with no observation of competing side reactions. We can reach at a better conclusion by comparing the results of the current method with those of some other related recent procedures for the reaction of benzaldehyde with cyclohex-2-enone, as summarized in the Table 3.

Table 2. BH reactions of 1 with various aldehydes.

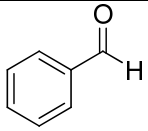
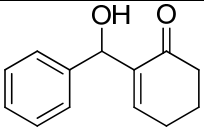
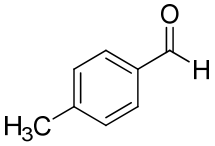
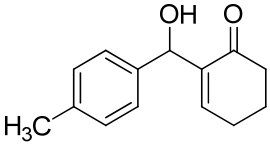
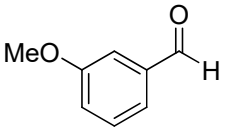
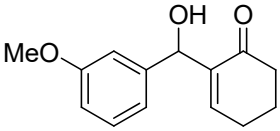
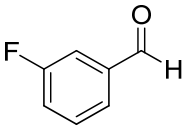
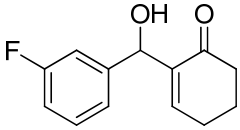
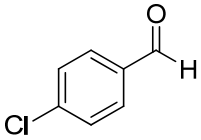
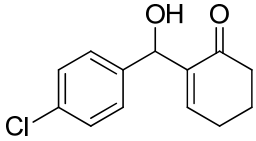
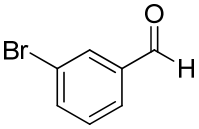
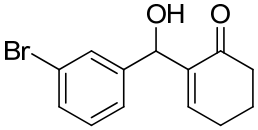
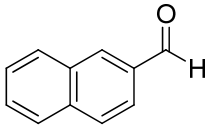
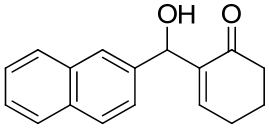
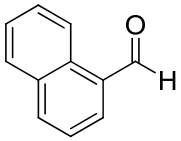
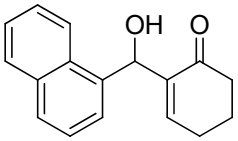
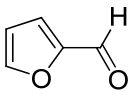
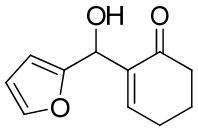
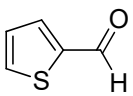
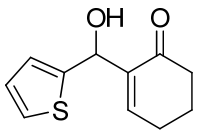
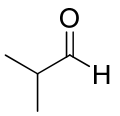
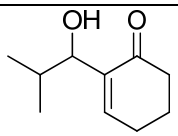
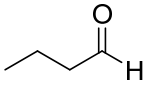
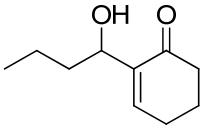
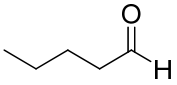
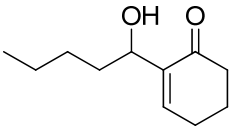
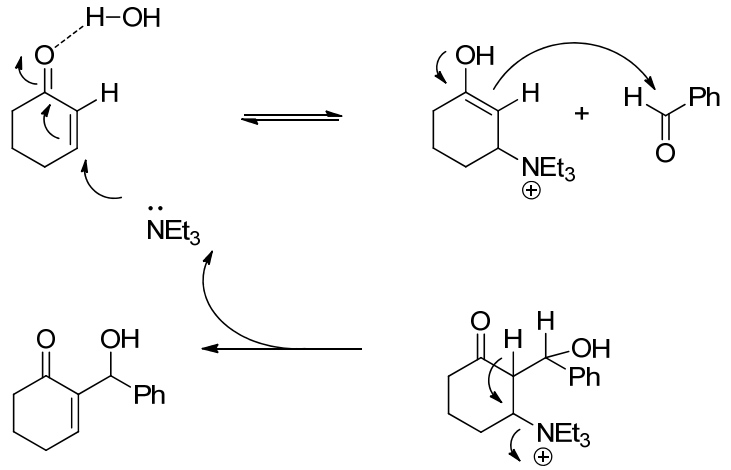
Entry	Aldehyde	Product		Time (h)	Yield (%)	Ref.
1			**3a**	24	81	[29]
2			**3b**	24	71	[30]
3			**3c**	20	77	[30]
4			**3d**	18	75	[28]
5			**3e**	15	81	[31]
6			**3f**	15	86	This work
7			**3g**	24	77	[32]
8			**3h**	24	76	[33]
9			**3i**	24	78	This work
10			**3j**	24	78	[32]

Table 2. *(Continued)*.

11			**3k**	18	81	[31]
12			**3l**	15	78	[28]
13			**3m**	15	81	[34]

[a]Isolated yield.



Scheme 2. Possible mechanism of the reaction.

Table 3. Comparison of various methods for the synthesis of **3a.**

Entry	Conditions	Yield (%)	Ref.
1	Et_3N/H_2O, 24 h	81	This work
2	DABCO/Schreiner's catalyst, 24 h	60	[36]
3	MgO/MeOH/65 °C, 24 h	60	[37]
4	4-dimethylaminopyridine/$Me_2N(CH_2)_2NMe_2$ MgI_2/MeOH/48 h	89	[38]
5	Et_2AlI/CH_2Cl_2/0 °C/24 h	65	[29]
6	1*H*-imidazole/$NaHCO_3$/THF/H_2O/90 h	45	[31]
7	$Me(CH_2)_{10}CH_2OSO_3Na$ 6,7-dihydro-5*H*-pyrrolo[1,2-a]imidazole/H_2O/22 h	92	[30]

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