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The Morita–Baylis–Hillman reaction in aqueous–organic solvent system

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ABSTRACT

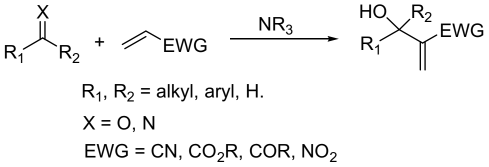
We have found that water and organic solvents mixed at different proportions can give good to excellent yields and short reaction times for the Morita–Baylis–Hillman reaction. The present Letter details our findings in the Morita–Baylis–Hillman reaction between several aromatic aldehydes and methyl acrylate or acrylonitrile. The selection of the catalyst was also evaluated and DABCO afforded the best results when compared to DBU, DMAP, HMT, Imidazole and Triethylamine.

1. Introduction

The Morita–Baylis–Hillman[1–4] reaction is an important way for C–C bond formation. It involves the coupling of alkenes containing electron-withdrawing groups (EWG) with aldehydes, ketones or imines, among others. Tertiary amines are used as nucleophilic catalysts where 1,4-diazabicyclo[2.2.2]octane (DABCO) is the most widely used (Scheme 1). [5,6]

The Morita–Baylis–Hillman adducts have been extensively used as intermediates in organic synthesis for a variety of applications, many of which have biologically activity.[7–14] Due to their synthetic potential, several protocols have been proposed to accelerate this reaction, such as the use of microwaves,[15] ultrasound,[16] addition of salts,[17] high pressure,[18] protic media[19] and ionic liquids.[20]

In our continuous search for efficient methodologies for the Morita–Baylis–Hillman reaction,[11–14,20,21] we have found that aqueous organic solvents give good yields and short reaction times.



Scheme 1. The Morita–Baylis–Hillman reaction.

This present Letter details our findings in the Morita–baylis–Hillman reaction between several aldehydes and methyl acrylate or acrylonitrile.

First, the reaction between *p*-nitrobenzaldehyde (**1a**), acrylonitrile (**2a**) and DABCO was examined in polar protic solvents (Table 1, entries 1–3), where the best result was obtained in *tert*-butanol (Table 1, entry 3). Following this initial study, we investigated different proportions of a *tert*-butanol/water system (Table 1, entries 4–11), as the presence of water is known to accelerate the Morita–Baylis–Hillman.[22,23] The effect of DABCO concentration was also evaluated.

The result obtained in entry 7 (Table 1) shows a great improvement on reaction time for the reaction carried in *tert*-butanol/water (60:40) in comparison with entry 3 (Table 1). This study also shows the dependence of reaction time on DABCO concentration (Table 1, entries 7–9). With an increased amount of DABCO, the reaction time can be greatly reduced and furnished on excellent yield of product.

Given the interesting results, we have explored the use of other nucleophilic catalyst for the Morita–Baylis–Hillman reaction on *tert*-butanol/water system (Table 2, entries 1–6). In addition, the use of a less reactive Michael acceptor, methyl acrylate (**2b**) and less reactive electrophile, benzaldehyde (**1b**) and anisaldehyde (**1c**) were evaluated. The results are summarized in Table 2 (entries 7–11).

The use of DABCO (Table 2, entry 1) gave better results than the use of other tertiary amines such as triethylamine, imidazole, DMAP, HMT and DBU (Table 2, entries 2–6). These results lead us to use DABCO in the reactions between different Michael acceptors and aromatic aldehydes increasing the scope of this reaction

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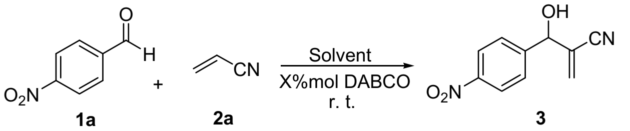
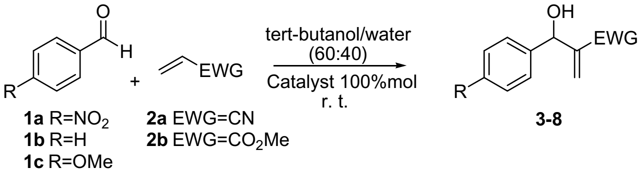
Table 1
Reaction between *p*-nitrobenzaldehyde (**1a**), acrylonitrile (**2a**) and DABCO (X mol %) in different polar protic solvents and water systems



Entry	Solvent[a]	DABCO (mol %)	Time	Yield[b] (%)
1	MeOH	100	24 h	55
2	*i*-PrOH	100	24 h	67
3	*tert*-BuOH	100	6 h	81
4	*tert*-BuOH/water (90:10)	100	1 h	94
5	*tert*-BuOH/water (90:10)	50	3 h	82
6	*tert*-BuOH/water (90:10)	10	4 h	77
7	*tert*-BuOH/water (60:40)	100	20 min	>99
8	*tert*-BuOH/water (60:40)	50	2 h	>99
9	*tert*-BuOH/water (60:40)	10	12 h	85
10	*tert*-BuOH/water (50:50)	100	2 h	87
11	*tert*-BuOH/water (40:60)	100	6 h	62

[a] Five millilitres of solvent were used.
[b] Isolated yields.

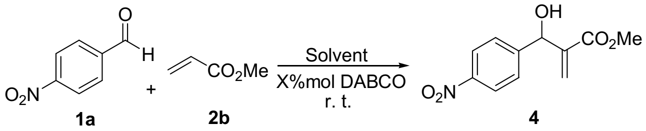
Table 2
Reaction between aromatic aldehydes (**1a**–**h**), Michael acceptors (**2a**–**b**) and catalyst (100 mol %) in *tert*-butanol/water (60:40) system



Entry	R	EWG	Catalyst	Time	Yield[a] (%)
1	NO_2 (**1a**)	CN (**2a**)	DABCO	20 min	**3**, >99
2	NO_2 (**1a**)	CN (**2a**)	Triethylamine	3 h	**3**, >99
3	NO_2 (**1a**)	CN (**2a**)	Imidazole	24 h	**3**, 22
4	NO_2 (**1a**)	CN (**2a**)	DMAP	24 h	**3**, 51
5	NO_2 (**1a**)	CN (**2a**)	HMT	24 h	**3**, 60
6	NO_2 (**1a**)	CN (**2a**)	DBU	24 h	**3**, 37
7	NO_2 (**1a**)	CO_2Me (**2b**)	DABCO	9 h	**4**, 92
8	H (**1b**)	CN (**2a**)	DABCO	24 h	**5**, 92
9	H (**1b**)	CO_2Me (**2b**)	DABCO	24 h	**6**, 79
10	OMe (**1c**)	CN (**2a**)	DABCO	24 h	**7**, 76
11	OMe (**1c**)	CO_2Me (**2b**)	DABCO	48 h	**8**, 55
12	F (**1f**)	CN (**2a**)	DABCO	48 h	**11**, 66
13	F (**1f**)	CO_2Me (**2b**)	DABCO	48 h	**12**, 57
14	OH (**1g**)	CN (**2a**)	DABCO	48 h	**13**, 70
15	OH (**1g**)	CO_2Me (**2b**)	DABCO	48 h	**14**, 61
16	CF_3 (**1h**)	CN (**2a**)	DABCO	48 h	**15**, 78

[a] Isolated yields.

Table 3
Reaction between *p*-nitrobenzaldehyde (**1a**) and methyl acrylate (**2b**) under DABCO catalysis (X mol %)



Entry	Solvent[a]	DABCO (mol %)	Time	Yield[b] (%)
1	MeOH	100	24 h	66
2	THF	100	48 h	63
3	DMSO	100	5 h 30 min	96
4	DMSO	50	9 h	85
5	DMSO	10	15 h	85
6	DMF	100	5 h 30 min	86
7	MeCN	100	5 h 30 min	90
8	CH_2Cl_2	100	24 h	15

[a] Five millilitres of solvent were used.
[b] Isolated yields.

methodology (Table 2, entries 7–16). Table 2 shows that less reactive aromatic aldehydes can give moderated to good yields (entries 8–11) in shortened reaction times.

The reaction time observed for the reaction between *p*-nitrobenzaldehyde (**1a**) and methyl acrylate (**2b**) under DABCO catalysis in the *tert*-butanol/water (60:40) system (Table 2, entry 7) was much longer to that observed for the reaction between *p*-nitrobenzaldehyde (**1a**) and acrylonitrile (**2a**) under the same conditions (Table 2, entry 1). These results prompted us to search for alternative reaction media for the reaction between *p*-nitrobenzaldehyde (**1a**) and methyl acrylate (**2b**) (Table 3).

In Table 3, it is shown that solvents of higher dielectric constants afforded better yields and shorter reaction times (entries 3, 6 and 7). DMSO was chosen solvent to investigate the effect of DABCO concentration on the reaction time, for the reaction of *p*-nitrobenzaldehyde (**1a**) and methyl acrylate (**2b**). Once again, 100 mol % of DABCO results in a 60% reduction of the reaction time and gives better yields (Table 3, entry 3).

Given the beneficial effect of water, the following aqueous systems were evaluated: DMSO/water, DMF/water and MeCN/water for the reaction between aromatic aldehydes (**1a**–**e**) and methyl acrylate (**2b**), under DABCO catalysis (100 mol %) (Table 4).

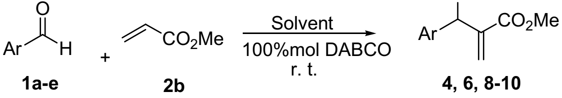
Table 4 shows that DMSO/water, DMF/water and MeCN/water systems promote a small improvement on reaction time for more reactive aldehydes (Table 4, entries 1–3). However, the DMSO/water system showed a large reduction in reaction time for less reactive aldehydes that also gave better yields of products (Table 4, entries 4–7).

Different proportions of the DMSO/water, DMF/water and MeCN/water systems were also evaluated in the reaction of less activated aldehydes, and the results are summarized in Table 5.

Table 5 shows that different proportions of DMSO/water, DMF/water and MeCN/water systems in the reaction between piperonal (**1d**) and methyl acrylate (**2b**) under DABCO catalysis do not lead to improvement on reaction time and yield when compared with entry 6, Table 4.

The role of water in the Morita–Baylis–Hillman mechanism can be rationalized as suggested by Aggarwal and co-workers[24] in their results on the theoretical calculations of the Morita–Baylis–Hillman mechanism. They predict that in the absence of protic solvents deprotonation of the α-position is the rate-determining step and occurs through a cyclic transition state, with proton

Table 4
Reaction between aromatic aldehydes (**1a**–**e**), methyl acrylate (**2b**) and DABCO in solvent/water (60:40) system



Entry	Aldehyde	Solvent[a]	Time	Yield[b] (%)
1	*p*-Nitrobenzaldehyde (**1a**)	DMSO/water	2 h 30 min	**4**, 90
2	*p*-Nitrobenzaldehyde (**1a**)	DMF/water	3 h 30 min	**4**, 91
3	*p*-Nitrobenzaldehyde (**1a**)	MeCN/water	5 h	**4**, 86
4	Benzaldehyde (**1b**)	DMSO/water	3 h 30 min	**6**, 95
5	Anisaldehyde (**1c**)	DMSO/water	8 h	**8**, 66
6	Piperonal (**1d**)	DMSO/water	15 h	**9**, 85
7	Naftaldehyde (**1e**)	DMSO/water	12 h	**10**, 95

[a] Five millilitres of solvent were used.
[b] Isolated yields.