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Journal of Molecular Catalysis A: Chemical 258 (2006) 251–256
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
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Pyridinium ionic liquids-accelerated amine-catalyzed Morita–Baylis–Hillman reaction

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Received 7 March 2006; received in revised form 11 May 2006; accepted 12 May 2006
Available online 5 July 2006

Abstract

Several ionic liquids were used for Morita–Baylis–Hillman reaction; the results show that the pyridinium ionic liquids *N*-ethylpyridinium tetrafluoroborate ([EPy][BF_4]) and *N*-butylpyridinium nitrate ([BuPy][NO_3]) as reaction media were efficient for DABCO-catalyzed Morita–Baylis–Hillman reaction. In short reaction time, good yields have been obtained. In addition, in the presence of ionic liquid [EPy][BF_4], the hexamethylenetetramine (HMTA), a cheap tertiary amine, effectively catalyzed the Morita–Baylis–Hillman reaction.

Keywords: Ionic liquids; Morita–Baylis–Hillman reaction; DABCO; HMTA

1. Introduction

The Morita–Baylis–Hillman reaction is one of the most versatile carbon–carbon bond-forming reactions in modern organic synthesis and has drawn considerable attention in the past decade due to its many advantages in regard to atomic economy, nonmetal catalysis, mild conditions, compatibility with multiple functional groups, and so on [1]. Unfortunately, however, there are a number of problems commonly associated with this useful reaction, most notably, its slow reaction rates (especially for acrylates, reaction times of one week or more are common) and low to moderate yields (especially when acrylic esters or acrylonitriles are used as Michael acceptors because of hydrolysis in aqueous media)[2]. To overcome these problems, several modifications have been attempted including new catalysts [3], novel solvent media such as supercritical CO_2 [4], ultrasound [5], high pressure [6], microwave irradiation [7] and hydrogen bonding effects (having a hydroxyl group in the catalyst or in the substrate) [8]. However, there still remains scope for identifying new methods for Morita–Baylis–Hillman reactions.

Ionic liquids, as a new class of solvents, possess a number of interesting properties. Especially their lack of vapor pressure, a widely accessible temperature range with lack of flammability and ease of reuse. Recently, Ionic liquids are attracting increasing interest as environmentally benign reaction media for organic synthesis [9]. The reactions already successfully carried out in ionic liquids include Diels–Alder, [10] Wittig, [11] Suzuki cross-coupling [12] and Heck reactions. [13] A recent report has described acceleration of the DABCO-catalyzed Morita–Baylis–Hillman reaction in an ionic liquid 1-*n*-butyl-3-methyimidazolium hexafluorophosphate ([bmim][PF_6]) [14]. However, it was later shown that the imidazolium salts, incorporating a hydrogen substituent at the C-2 position, are deprotonated under mildly basic conditions, forming the corresponding carbenes, which can cause undesired side reactions [15]. This undesired deprotonation has been partly overcome by the application of imidazolium salts with a methyl group at the C-2 position (1-butyl-2,3-dimethylimidazolium) [16] or a phenyl ring at the C-2 position (1,3-dimethyl-2-phenylimidazolinium) [17], in the Baylis–Hillman reaction. However, the need for the efficient ionic liquid used for Morita–Baylis–Hillman reaction still stimulates a continuous research effort.

In our laboratories, we have been looking at the development of ionic liquids that can be used for the Morita–Baylis–Hillman reaction. During our own investigations on non-imidazolium-based ionic liquids, we have recently found that the ionic liquid *N*-butylpyridinium tetrafluoroborate ([BuPy][BF_4]) qualifies as an efficient, recyclable reaction medium for

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doi:10.1016/j.molcata.2006.05.032

the Morita–Baylis–Hillman reaction [18]. In the continuation of our ongoing program to develop environmentally benign methods using ionic liquids as novel promoters, Herein, we would like to present the other possible alternative ionic liquids *N*-ethylpyridinium tetrafluoroborate ([EPy][BF_4]) and *N*-butylpyridinium nitrate ([BuPy][NO_3]) for the Morita–Baylis–Hillman reaction: for many substrates the above ionic liquids could be efficient solvent media at room temperature without any protection.

2. Results and discussion

In order to explore more ionic liquids used for the Morita–Baylis–Hillman reaction, many ionic liquids, such as 1-benzyl-1,4-diazabicyclo[2.2.2]octane phosphate ([BZDABCO]$_3$[PO_4]), 1-butylpyridinium nitrate ([BuPy][NO_3]), 1-benzylpyridinium tetrafluoroborate ([BZPy][BF_4]), 1-butyl-1,4-diazabicyclo[2.2.2]octane phosphate ([BDABCO]$_3$[PO_4]), 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) and 1-ethylpyridinium tetrafluoroborate ([EPy][BF_4]), were synthesized according to literature procedure [19] and employed as Morita–Baylis–Hillman reaction media; First, we examined the efficacy of these ionic liquids in the formation of 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile by the Morita–Baylis–Hillman reaction of 4-nitrobenzaldehyde with acrylonitrile. The results are summarized in Table 1. When [BZPy][BF_4], [BDABCO]$_3$[PO_4] or [BZDABCO]$_3$[PO_4] were employed as a reaction medium, no reaction occurred after stirring for 48 h (Table 1, entries 3–5). Performing the same reaction in the ionic liquid [bmim][BF_4], 4-nitrobenzaldehyde was consumed within 12 h with the desired product isolated in only 48% yield (Table 1, entry 6). As a comparison, the same reaction in the common molecular solvents, such as acetonitrile and tetrahydrofuran (THF), gave 32 and 40% yields after 48 h (Table 1, entries 1–2). We surprisingly found that the same reaction in [EPy][BF_4] ionic liquid gave 92% yield of the desired product in 2 h (Table 1, entry 8) and the same reaction in [BuPy][NO_3] ionic liquid gave 78% yield of desired product in 5 h (Table 1, entry 7). When the same reaction (Table 1, entry 9) was conducted under nitrogen atmosphere, the same result was obtained. However, when only 0.5 mmol of DABCO was used, relatively longer reaction time (3.5 h) was needed (Table 1, entry 10). The above results clearly demonstrate that the Morita–Baylis–Hillman reaction of 4-nitrobenzaldehyde with acrylonitrile can be greatly accelerated in the ionic liquid [EPy][BF_4] or [BuPy][NO_3] without any protection.

Table 1
Morita–Baylis–Hillman reactions of 4-nitrobenzaldehyde with acrylonitrile in different solvents[a,b,c]

Entry	Solvent	Time (h)	Product yield (%)
1	CH_3CN	48	32
2	THF	48	40
3	[BDABCO]$_3$[PO_4]	48	N/A[d]
4	[BZDABCO]$_3$[PO_4]	48	N/A[d]
5	[BZPy][BF_4]	48	N/A[d]
6	[bmim][BF_4]	12	48
7	[BuPy][NO_3]	5	72
8	[EPy][BF_4]	2	92
9	[EPy][BF_4]	2	92[e]
10	[EPy][BF_4]	3.5	92[f]

[a] Reactions were run with 4-nitrobenzaldehyde (3 mmol), acrylonitrile (6 mmol) and DABCO (1 mmol) at room temperature.
[b] Isolated yield based on 4-nitrobenzaldehyde.
[c] The reaction was monitored by thin layer chromatography (TLC) analysis.
[d] Only trace amount of product was detected and its yield not determined.
[e] The reaction was conducted under nitrogen atmosphere.
[f] Reaction was run with 4-nitrobenzaldehyde (3 mmol), acrylonitrile (6 mmol) and DABCO (0.5 mmol).

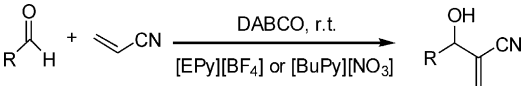
The reason for the reactivity increase in ionic liquid in relation to the common molecular solvent could be attributed to stabilization of the zwitterionic intermediate, generated from the Michael addition of a nucleophilic Lewis base to an activated alkene. This intermediate can be maintained in high concentration in the ionic liquid, which may lead to acceleration of the nucleophilic attack of the zwitterionic intermediate to the aldehyde, giving the Morita–Baylis–Hillman adduct. As a result, the reaction rate can be accelerated.

In a recent paper, Gong and coworkers employed the ionic liquid [EPy][BF_4] in the Morita–Baylis–Hillman reaction [20]. Since the melting point of [EPy][BF_4] is 53 °C, in order to keep the reaction proceeding in one phase, they keep the reaction temperature at 60 °C; in addition, all reactions were conducted under nitrogen atmosphere. In our study on the preparation of the ionic liquid [EPy][BF_4], we found that a small quantity of $NaBF_4$ dissolved in ionic liquid [EPy][BF_4] can lower the melting point of the ionic liquid [EPy][BF_4] to room temperature. In the Morita–Baylis–Hillman reaction mixture it remained permanently a liquid. Thus the Morita–Baylis–Hillman reaction in the ionic liquid [EPy][BF_4] with a small quantity of $NaBF_4$ can be conducted at room temperature. So excess $NaBF_4$ (1.2 eq.) was used in the preparation of ionic liquid [EPy][BF_4].

In order to test the generality of ionic liquids [EPy][BF_4] and [BuPy][NO_3] as media for the Morita–Baylis–Hillman reaction, various aldehydes were allowed to react with acrylonitrile in the presence of DABCO, as shown in Table 2. The Morita–Baylis–Hillman reactions of aliphatic aldehydes (Table 2, entries 10, 11) gave moderate yields, while good to excellent yields of the desired products were obtained with aromatic aldehydes. Another important observation that needs special mention is that, regardless of the nature of aldehydes investigated, the reactions proceeded all with higher yields and shorter reaction time in the ionic liquid [EPy][BF_4] than in [BuPy][NO_3] ionic liquid at room temperature. Thus the ionic liquid [EPy][BF_4] was more suitable for the Morita–Baylis–Hillman reaction. The reason is being actively investigated in our laboratory.

Aiming to increase the scope of our methodology, we next used methyl acrylate as the Michael acceptor for this reaction, and the results are summarized in Table 3. Higher yields at shorter reaction times were achieved. Interestingly, less reactive 4-hydroxy-3-methoxybenzaldehyde (Table 3, entry 9) also

Table 2
Morita–Baylis–Hillman reactions of aldehydes with acrylonitrile[a]



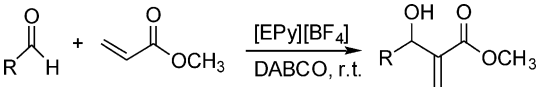
Entry	*R*	[EPy][BF_4][b]		[BPy][NO_3]	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1	C_6H_5	1	79	6	66
2	2-$O_2NC_6H_4$	0.5	89	5	72
3	3-$O_2NC_6H_4$	0.5	84	5	75
4	4-$O_2NC_6H_4$	2	92	5	78
5	4-ClC_6H_4	1	86	4	82
6	2,4-$Cl_2C_6H_3$	0.75	87	4	83.5
7	4-Cl-3-$O_2NC_6H_3$	0.5	93	3	86
8	3-OHC_6H_4	3.5	73.5	10	64
9	4-OH-3-$CH_3OC_6H_3$	10	64	12	60
10	CH_3	8	62	12	42
11	$CH_3CH_2CH_2$	8	63	12	51

[a] The reaction conditions were as follows: aldehyde (3 mmol), acrylonitrile (6 mmol), DABCO (1 mmol), [EPy][BF_4] (5 ml), room temperature; no further increase in yield after the report time.
[b] [EPy][BF_4] with a small quantity of $NaBF_4$.

afforded the desired product in 64% yield after 12 h, and simple aliphatic aldehydes worked well (Table 3, entries 10, 11). Thus the ionic liquid [EPy][BF_4] is indeed a very effective solvent media for all substrates tested.

To evaluate the possibility of recycling the ionic liquid used for the reaction, methyl acrylate (6 mmol) was added to a magnetically stirred solution of 3-nitrobenzaldehyde (3 mmol) and DABCO (1 mmol) in [EPy][BF_4](5 ml). After stirring for 4 h, the reaction mixture was extracted with ethyl ether (3 × 20 ml). The combined ethyl ether mixture was reduced to dryness in vacuo. Flash column chromatography was employed to purify the Morita–Baylis–Hillman adduct. Then methyl acrylate, 3-nitrobenzaldehyde and DABCO were added to the recycled [EPy][BF_4] for repeating the reaction. The recovered ionic liquid was used at least four times almost without reduction of reaction yields (Table 4).

Table 3
Morita–Baylis–Hillman reactions of aldehydes with methyl acrylate[a,b]



Entry	*R*	Time (h)	Yield (%)
1	C_6H_5	6	65
2	2-$O_2NC_6H_4$	3	76
3	3-$O_2NC_6H_4$	4	78
4	4-$O_2NC_6H_4$	4	83
5	4-ClC_6H_4	5	72
6	2-4-$Cl_2C_6H_3$	3	79.5
7	4-Cl-3-$O_2NC_6H_3$	2	76
8	3-OHC_6H_4	5	68
9	4-OH-3-$CH_3OC_6H_3$	12	64
10	CH_3	8	58
11	$CH_3CH_2CH_2$	8	60

[a] The reaction conditions were as follows: aldehyde (3 mmol), methyl acrylate (6 mmol), DABCO (1 mmol), [EPy][BF_4] (5 ml), room temperature; no further increase in yield after the report time.
[b] [EPy][BF_4] with a small quantity of $NaBF_4$.

Table 4
Reuse of the ionic liquid [EPy][BF_4][a]

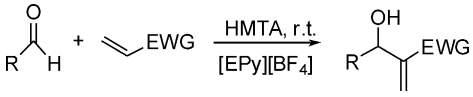
Cycle	Yield (%)	Cycle	Yield (%)
1	78	3	74
2	77	4	78

[a] All cycles were performed with 3-nitrobenzaldehyde (3 mmol), methyl acrylate (6 mmol), [EPy][BF_4] (5 ml) and DABCO (1 mmol) at room temperature.

Furthermore, we also attempted to use the hexamethylenetetramine (HMTA) as a catalyst for the catalyzed the Morita–Baylis–Hillman reaction in the ionic liquid [EPy][BF_4]. This was done because we want to find an alterative catalyst for the ionic liquid [EPy][BF_4]-accelerated Morita–Baylis–Hillman reaction. Since DABCO is an expensive tertiary amine, it is uneconomic to perform DABCO-catalyzed Morita–Baylis–Hillman reactions on an industrial scale. In contrast, HMTA, a very cheap tertiary amine, is a non-hygroscopic and stable reagent of low toxicity. In a recent paper, Vasconcellos et al. described the use of HMTA as a cheap alternative catalyst for the Morita–Baylis–Hillman reaction with DMSO as solvent [21], but the reaction time was generally long (1–16 days).

In our process, to achieve a meaningful comparison with the DABCO-catalyzed Morita–Baylis–Hillman reaction, we used the same reaction conditions, namely acrylonitrile (6 mmol) or methyl acrylate (6 mmol) with various aldehydes (3 mmol) in the presence of HMTA (1 mmol) at room temperature. The results are shown in Table 5. As can be seen from Tables 2, 3 and 5, in the same reaction conditions, the [EPy][BF_4] + DABCO is more efficient than the [EPy][BF_4] + HMTA. However, the system [EPy][BF_4] + HMTA is still efficient compared with the previous system [21]. This is dramatically demonstrated by the reaction between benzaldehyde and acrylonitrile. Using the previous system

Table 5
Morita–Baylis–Hillman reactions mediated by HMTA at room temperature in ionic liquid [EPy][BF_4][a]



Entry	*R*	EWG	Time (h)	Yield (%)[b]
1	C_6H_5	CN	8	76
2	C_6H_5	COOMe	12	61.5
3	4-$O_2NC_6H_4$	CN	5	88
4	4-$O_2NC_6H_4$	COOMe	8	83
5	4-Cl C_6H_4	CN	6	79
6	4-Cl C_6H_4	COOMe	12	62
7	4-Cl-3-$O_2NC_6H_3$	CN	5	90
8	4-Cl-3-$O_2NC_6H_3$	COOMe	8	70
9	3-OHC_6H_4	CN	20	67
10	CH_3	CN	20	53
11	$CH_2CH_2CH_3$	CN	20	56.5

[a] All reactions were performed with aldehydes (3 mmol), activated alkenes (6 mmol) in the ionic liquid [EPy][BF_4] (5 ml) in the presence of the catalyst HMTA (1 mmol) at room temperature. The reaction was monitored by TLC analysis.
[b] Refers to isolated, pure products after silica gel chromatograph.

tem [21], 69% yield was achieved after 16 days, but under our conditions we obtained 76% yield after just 8 h (Table 5, entry 1).

In summary, we have developed a highly efficient method for the preparation of Morita–Baylis–Hillman adducts by using ionic liquid [EPy][BF_4] and [BuPy][NO_3] as solvent media. The ionic liquid [EPy][BF_4] is more applicable to the Morita–Baylis–Hillman reactions of a variety of aldehydes, including electron-deficient and electron-rich aromatic aldehydes, and aliphatic aldehydes. Furthermore, using ionic liquid [EPy][BF_4] as a reaction media, we also examined the application of the cheap catalyst HMTA in the Morita–Baylis–Hillman reactions; short reaction time and good to excellent yields was obtained. In conclusion, the current method offers several advantages including mild reaction condition, short reaction time, high yield of the product, simple experimental procedure as well as the reusability of the ionic liquid, which makes it a useful and practical method for the syntheses of Morita–Baylis–Hillman adducts.

3. Experimental section

3.1. General remarks

All glassware was oven-dried and cooled in a desiccator (P_2O_5, desiccant) prior to use. Ionic liquids were prepared following reported procedures [19]. All melting points were recorded by a capillary melting point apparatus and uncorrected. The IR spectra were determined on an FTIR-8300S infrared spectrometer by dispersing samples in neat or KBr disks. ^{1}H NMR spectra were measured on a DRX300 NMR spectrometer using TMS as an internal standard with $CDCl_3$, D_2O or D-acetone as solvent. The elemental analyses were performed in the Institute of Chemistry, Chinese Academy of Sciences. Analytical thin layer chromatography (TLC) was carried out using MN Kieselgel G/UV_{254} (Art.816320) glass backed plates.

3.2. Preparation and characterization of ionic liquids

3.2.1. Preparation of ionic liquid [EPy]Br

N-Ethylpyridiniumbromide ([EPy]Br) was prepared according to a literature procedure [19a] with the following modifications. Excess bromoethane and pyridine were gently stirred together at room temperature (29 °C), in the dark, in a standard reflux apparatus fitted with a drying tube. Twenty-four hours later, the product appeared as white crystals. Then the product was dissolved in a minimum amount of boiling acetonitrile about 15 min later, the mixture was filtered under vacuum and approximately 10% by volume of ethyl acetate was added to the filtrate, which was left to cool, isolated from atmospheric moisture by a drying tube. White crystals of [EPy]Br were precipitated and these were filtered off at a vacuum pump and washed with ethyl acetate, and the excess solvent was removed under vacuum to give [EPy]Br in 97% yield. ^{1}H NMR (300 MHz, D_2O): δ = 8.71 (d, J = 7.6 Hz, 2H), 8.42 (t, 2H), 8.05 (t, 1H), 4.57 (q, 2H, N-CH_2), 1.84 (t, 3H, CH_3).

3.2.2. Preparation of ionic liquid [EPy][BF_4]

An anion exchange reaction from bromide to tetrafluoroborate (BF_4^-) was completed by mixing [EPy]Br and excess $NaBF_4$ (1.2 eq.) according to the literature [19a]. The reactants were gently stirred together for 12 h in acetone at room temperature (29 °C). Precipitated NaCl was filtered off and [EPy][BF_4] was dried under reduced pressure. Owing to the unreacted $NaBF_4$ dissolved in the ionic liquid [EPy][BF_4], the product is pale oil. The $NaBF_4$ are removed easily by redissolving the ionic liquid in dichloromethane, which cause the precipitation of the $NaBF_4$. Subsequent filtration to gives the product ionic liquid [EPy][BF_4] in 92% yield. White solid—mp: 53 °C (lit. [19a], mp 53–54 °C); IR (neat, cm^{-1}): 3446, 3112, 3023, 2956, 2938, 2876, 1632, 1346; ^{1}H NMR (300 MHz, D_2O): δ = 8.70 (d, J = 7.6 Hz, 2H), 8.41 (t, 2H), 8.02 (t, 1H), 4.52 (q, 2H, N-CH_2), 1.87 (t, 3H, CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 146.5, 146.1, 146.0, 128.5, 128.4, 59.0, 17.2.

3.2.3. Preparation of ionic liquid [BuPy] [NO_3]

[BuPy]Br was synthesized according to a literature procedure [19a]. The same synthetic procedure as for [EPy][BF_4] was followed to obtain [BuPy][NO_3] as a pale yellow oil in 91% overall yield. Pale yellow oil—IR (neat, cm^{-1}): 3467, 3132, 3063, 2964, 2938, 2876, 1635, 1489, 1464, 1342; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.47 (d, J = 8.6 Hz, 2H), 8.26 (t, 2H), 8.74 (t, 1H), 4.97 (t, 2H, N-CH_2), 0.97–2.07 (m, 7H, $CH_2CH_2CH_3$). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 146.4, 146.0, 146.1, 128.5, 128.3, 62.1, 32.9, 22.0, 14.1.

3.2.4. Preparation of ionic liquid 1-benzylpyridinium tetrafluoroborate ([BzPy][BF_4])

The same procedure was followed as for [BuPy]Br to obtain [BzPy]Cl as a white solid. The solid was redissolved in acetonitrile. After the solution was cooled, the crystal of the [BzPy]Cl were obtained in 86% yield, ^{1}H NMR (300 MHz, D-acetone): δ = 9.15 (d, J = 8.3 Hz, 2H), 8.66 (t, 1H), 8.19 (t, 2H), 7.59 (d, J = 7.3 Hz, 2H), 7.42 (d, J = 6.9 Hz, 3H), 5.95 (s, 2H).

The same procedure was followed as for [EPy][BF_4] to obtain [BzPy] [BF_4] as a pale oil in 83% yield; IR (neat, cm^{-1}): 3638, 3062, 3071, 1633, 1586, 1490, 1457, 1065; ^{1}H NMR shifts were the same as for [BzPy]Cl.

3.2.5. Preparation of ionic liquid [bmim] [BF_4]

The ionic liquid [bmim] [BF_4] was synthesized according to a literature procedure [19c]. It was obtained giving [bmim] [BF_4] as a pale yellow oil in 89% yield; ^{1}H NMR shifts correspond to those from the literature [19c]. IR (neat, cm^{-1}): 3163, 3122, 2965, 2939, 2877, 1575, 1468, 1171, 1072; ^{1}H NMR ($CDCl_3$, D_2O): δ = 8.75 (s, 1H), 7.43 (d, J = 2.1 Hz, 1H), 7.29 (d, J = 2.1 Hz, 1H), 4.19 (t, 2H), 3.92 (s, 3H), 1.84 (m, 2H), 1.35 (m, 2H), 0.95(t, 3H).

3.2.6. Preparation of ionic liquid 1-butyl-1, 4-diazabicyclo [2.2.2] octane phosphate ([BDABCO]$_3$[PO_4])

[BDABCO]$_3$[PO_4] was synthesized according to a literature procedure [19b]. *n*-Butyl chloride (11 ml, 0.1 mol) with the appropriate 1,4-diazabicyclo[2.2.2]octane (11.2 g, 0.1 mol)

were combined with EtOAc (50 ml) in a flask fitted with a magnetic stirrer. The reaction mixture was stirred at ambient temperature for 48 h; the resultant precipitate was collected by suction filtration through sintered glass, washed with EtOAc, anhydrous Et_2O and dried under high vacuum to give the product [BDABCO]Cl in 76% yield. White solid.

The [BDABCO]Cl (8.07 g, 0.05 mol) was dissolved in MeOH (50 ml) and to it was added 85% phosphoric acid (2.99 ml, 0.017 mol). The reaction mixture was heated at reflux for 24 h. All volatile materials were evaporated, first using a rotary evaporator, and then under high vacuum for 1 week. The product $[BDABCO]_3[PO_4]$ was obtained in 67% yield. Pale oil—^{1}H NMR (300 MHz, D_2O): $\delta = 3.75$(d, $J = 1.3$ Hz, 6H), 3.68 (t, 6H), 3.36 (q, 2H), 1.65 (t, 2H), 1.26 (q, 2H), 0.82 (t, 3H).

3.2.7. Preparation of ionic liquid 1-benzyl-1,4-diazabicyclo [2.2.2] octane phosphate ([BZDABCO]$_3$[PO$_4$])

$[BZDABCO]_3[PO_4]$ was synthesized according to a literature procedure [19b]; The same procedure was followed as for $[BDABCO]_3[PO_4]$ to obtain $[BZDABCO]_3[PO_4]$ as pale yellow oil—^{1}H NMR (300 MHz, D_2O): $\delta = 7.61$ (d, $J = 1.7$ Hz, 2H), 7.42 (d, $J = 1.5$ Hz 3H), 5.09 (s, 2H), 3.73 (t, 6H), 3.15 (t, 6H).

3.3. General procedure for the Morita–Baylis–Hillman reaction

A solution of aldehyde (3 mmol) and activated alkene (6 mmol) in 5 ml of ionic liquid was stirred at room temperature (25–29 °C) in the presence of DABCO (1 mmol) or HMTA (1 mmol), the progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was extracted with ethyl ether (3 × 20 ml). Then the combined ethyl ether fractions were evaporated. The crude products thus obtained were purified by flash column chromatography (silica gel, 200–300 mesh; ethyl acetate/petroleum ether, 1:5–1:3). All desired products were characterized by IR and ^{1}H NMR. The ionic liquid was directly used in the next run.

3.4. Characterization of the Morita–Baylis–Hillman reaction adducts

3-Hydroxy-2-methylene-3-(2,4-dichlorophenyl)propanenitrile (Table 2, entry 6). White solid—mp: 74 °C. IR (KBr, cm^{-1}): 3384.8, 2229.6, 1527.5, 1348.1 cm^{-1}. ^{1}H NMR (300 Mz, $CDCl_3$): $\delta = 7.55$ (d, $J = 8.01$ Hz, 1H), 7.39 (s, 1H), 7.28 (d, $J = 7.5$ Hz, 1H), 6.05 (s, 2H), 5.67 (s, 1H), 3.07 (br s, 1H). ^{13}C NMR (300 Mz, $CDCl_3$): $\delta = 72.55$, 118.87, 126.70, 130.38, 131.37, 131.97, 134.09, 135.60, 137.60, 142.58. Anal. calcd. for $C_{10}H_7Cl_2NO$: C, 52.63; H, 3.07; N, 6.14. Found: C, 52.58; H, 3.05; N, 6.12.

3-Hydroxy-2-methylene-3-(3-hydroxyphenyl)propanenitrile (Table 2, entry 8). Yellow oil—IR (neat, cm^{-1}): 3381.0, 2233.4, 1593.5, 1271.0 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.25$ (t, $J = 7.86$ Hz, 1H), 6.88 (d, $J = 7.06$ Hz, 2H), 6.80 (d, $J = 7.01$ Hz, 1H), 6.7 (br s, 1H), 6.10 (s, 1H), 6.04 (s, 1H), 5.90 (br s, 1H), 5.25 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 73.8$, 113.2, 113.5, 116.0, 116.8, 118.6, 128.8, 130.2, 140.7, 156.0. Anal. calcd. for $C_{10}H_9NO_2$: C, 68.57; H, 5.14; N, 8.01. Found: C, 68.51; H, 5.22; N, 7.86.

3-Hydroxy-2-methylene-3-(3-hydroxyphenyl)propanoic acid, methyl ester (Table 3, entry 8). Pale yellow solid—mp: 103 °C. IR (KBr, cm^{-1}): 3411.8, 3090.6, 2852.5, 1708.8, 1589.2, 1047.3, 952.8 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.18$ (t, $J = 7.56$ Hz, 1H), 6.90 (d, $J = 7.32$ Hz, 2H), 6.78 (t, $J = 7.21$, 1H), 6.33 (s, 1H), 5.82 (s, 1H), 5.49 (s, 1H), 4.23 (s, 1H), 3.72 (s, 3H), 2.78 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 54.5$, 75.6, 115.2, 115.8, 116.4, 117.3, 121.5, 128.9, 132.0, 114.5, 158.2. Anal. calcd. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.77. Found: C, 63.41; H, 5.78.

3-Hydroxy-2-methylene-3-(4-chloro-3-nitrophenyl)propanenitrile (Table 2, entry 7). Yellow oil—IR (neat, cm^{-1}): 3429.2, 2875.6, 2229.6, 1537 cm^{-1}. ^{1}H NMR (300 Mz, $CDCl_3$): $\delta = 7.74$ (s, 1H), 7.39 (m, 2H), 6.00 (s, 1H), 5.92 (s, 1H), 5.20 (s, 1H), 3.00 (br s, 1H). ^{13}C NMR (300 Mz, $CDCl_3$): $\delta = 74.73$, 118.67, 126.01, 127.53, 129.72, 133.54, 133.94, 134.61, 142.14, 150.38. Anal. calcd. for $C_{10}H_7ClN_2O_3$: C, 50.31; H, 2.94; N, 11.74. Found: C, 50.26; H, 2.91; N, 11.72.

3-Hydroxy-2-methylene-3-(4-chloro-3-nitrophenyl)propanoic acid, methyl ester (Table 3, entry 7). White solid—mp: 84 °C. IR (KBr, cm^{-1}): 3471.6, 1708.8, 1533.3 cm^{-1}. ^{1}H NMR (300 Mz, $CDCl_3$): $\delta = 7.89$ (s, 1H), 7.48–7.55 (m, 2H), 6.39 (s, 1H), 5.89 (s, 1H), 5.55 (s, 1H), 3.73 (s, 3H), 3.01 (br s, 1H). ^{13}C NMR (300 Mz, $CDCl_3$): $\delta = 54.72$, 74.56, 126.04, 128.57, 128.88, 129.90, 133.58, 134.22, 143.01, 144.53, 168.69. Anal. calcd. for $C_{11}H_{10}ClNO_5$: C, 48.62; H, 3.68; N, 5.16. Found: C, 48.35; H, 3.71; N, 5.12.

The other Morita–Baylis–Hillman reaction products were reported in the literatures [2a,3j,3k,14,21]. Their structures were confirmed by mp, IR and H^1 NMR data.

Acknowledgements

Financial support from the Foundation of Xinzhou Teachers University (no. [2005] 89), the Natural Science Foundation of Shanxi Province (no. [2005] 1028, and the Returned Overseas Chinese Scholars Foundation of Ministry of Education of China (no. [2005] 383) are gratefully acknowledged.

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