Asian Journal of Chemistry Vol. 18, No. 2 (2006), 840–844

Rate Acceleration of Baylis-Hillman Reaction with Lithium Bromide and 1,8-Diazabicyclo[5.4.0]undec-7-ene in Solvent Free Medium

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The Baylis-Hillman reaction was accelerated in the presence of catalytic amount of lithium bromide and 1,8-diazabicyclo[5.4.0]-undec-7-ene in a solvent free medium. A preliminary kinetic study revealed that the relative rate of the reaction using lithium bromide was considerably faster than that of reaction without lithium bromide.

Key Words: Baylis-Hillman, β-hydroxy-α-methylene esters, Lithium bromide, 1,8-Diazabicyclo[5.4.0]undec-7-ene

INTRODUCTION

The Baylis-Hillman reaction, *i.e.*, the coupling of aldehydes and activated vinyl compounds, is one of the most important carbon-carbon bond forming reactions in organic synthesis[1]. This reaction is commonly used for the coupling of Michael acceptors with aldehydes to give β-hydroxy-α-methylene esters/ketones/nitriles. Imines[2] and imunium salts[3] have also occasionally been employed as electrophiles in place of aldehyde in this reaction providing a useful and rapid entry to the corresponding products.

In recent years, progress has been made in the implementation of Baylis-Hillman reaction, since their first report on the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of 1,4-diazabicyclo[2.2.2]-octane (DABCO)[4]. The Baylis-Hillman-Type C-C single bond formation has become an active area in synthethic organic chemistry. This reaction is an exquisite reaction. The cheap and readily available starting materials are converted, using a suitable catalyst, into functionalized products. However, the reaction suffers from poor reaction rates and many research groups have examined a variety of methods to accelerate the reaction.

Several attempts have been made to increase the rate of the reaction through either physical or chemical means, but there are disadvantages associated with most of the methods[5].

Recently, various methods for the acceleration of Baylis-Hillman reaction have been developed with certain limitations[6]. One of the most important methods is the salt effect using Lewis acid as co-catalyst. The combination of lithium perchlorate

($LiClO_4$) and DABCO in ether[7], use of Et_2AlI in CH_2Cl_2[8], Lewis base effects including 4-(dimethylamino)pyridine (DMAP), tributyl phosphine and DBU in the Baylis-Hillman reaction were examined[9].

EXPERIMENTAL

Chemicals were purchased from Merck and Fluka. Elemental analyses were performed using a Heraeus CHN-O-rapid analyzer. IR spectra were determined on a Shimadzu IR-470 spectrometer. ^1H NMR spectra were recorded on a Bruker AC, FT-NMR (80 MHz) in $CDCl_3$ with tetramethylsilane (TMS). Preparative thin layer chromatography was prepared from Merck Kieselgel 60 H, F_{254}, Art. No. 7730. GC was carried out using Buck Scientific 910 (capillary column, MXT-5, 15 m). All solvents used were dried and distilled according to standard procedures.

Synthesis of 2-(hydroxy-aryl-methyl)-acrylic acid methyl esters (2): To a stirred mixture of methyl acrylate (0.45 mL, 5.0 mmol), LiBr (0.435 g, 5.0 mmol) and arylaldehyde (5.0 mmol) at –10°C under nitrogen was slowly added DBU (0.74 mL, 5.0 mmol). The reaction was allowed to warm up to room temperature and after the desired time, the reaction mixture was diluted with ether (25 mL) and washed with HCl (2 M, 15 mL) followed by water (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide a crude mixture. The mixture was purified by column chromatography eluting with petroleum ether/diethyl ether (4 : 1) to give the adducts **2a–g.**

2b: Pale green oil, yield 93%; IR (KBr, cm^{-1}): 3460 ν(O—H), 1725 ν(C=O), 1625 ν(C=C); Anal. calculated for $C_{10}H_{11}NO_3$ (Found: C, 62.20; H, 5.84; N, 7.19; requires C, 62.17; H, 5.74; N, 7.25%); ^1H NMR (80 MHz, $CDCl_3$): δ = 2.9 (br, OH), 3.72 (s, OCH_3), 5.55 (s, CH), 5.83 (s, 1H), 6.30 (s, 1H), 7.30–8.64 (m, 4H) ppm.

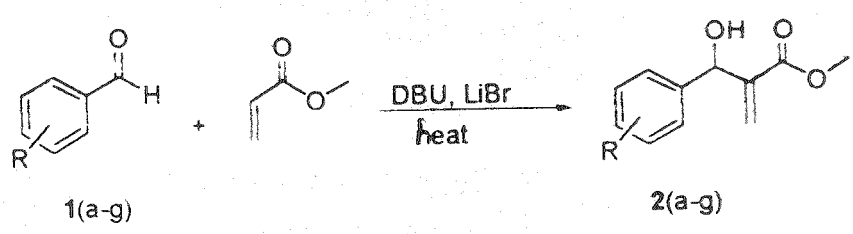
2c: Pale yellow solid, m.p. = 39–40°C, yield 90%; IR (KBr, cm^{-1}): 3450 ν(O—H), 1722 ν(C=O), 1622 ν(C=C); Anal. calculated for $C_{11}H_{11}ClO_3$ (Found: C, 58.20; H, 4.84; Cl, 15.60; requires C, 58.29; H, 4.89; Cl, 15.64%); ^1H NMR (80 MHz, $CDCl_3$): δ = 2.75 (br, OH), 3.71 (s, OCH_3), 5.55 (s, CH), 5.81 (s, 1H), 6.31 (s, 1H), 7.10–7.24 (m, 4H) ppm.

2e: Yellow oil, yield 94%; IR (KBr, cm^{-1}): 3460 ν(O—H), 1729 ν(C=O), 1630 ν(C=C); Anal. calculated for $C_{12}H_{14}ClFO_3$ (Found: C, 55.20; H, 5.35; Cl, 13.56; F, 7.20; requires C, 55.29; H, 5.41; Cl, 13.60; F, 7.29%); ^1H NMR (80 MHz, $CDCl_3$): δ = 2.64 (br., OH), 3.76 (s, OCH_3), 5.54 (s, CH), 5.82 (s, 1H), 6.36 (s, 1H), 6.90–7.29 (m, 3H) ppm.

RESULTS AND DISCUSSION

Recently Aggarwal and co-workers[10] reported that 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) is in fact the optimum catalyst for the Baylis-Hillman reaction, providing adducts at much faster rates than using DABCO, 3-hydroxyquinoclidine (3-HDQ) and other catalysts.

In continuation of our interest for Baylis-Hillman adducts[11] and mechanistic studies of this reaction, herein we wish to report our novel methodology for the acceleration of Baylis-Hillman reaction with LiBr/DBU in a solvent free medium (**Scheme-1**).

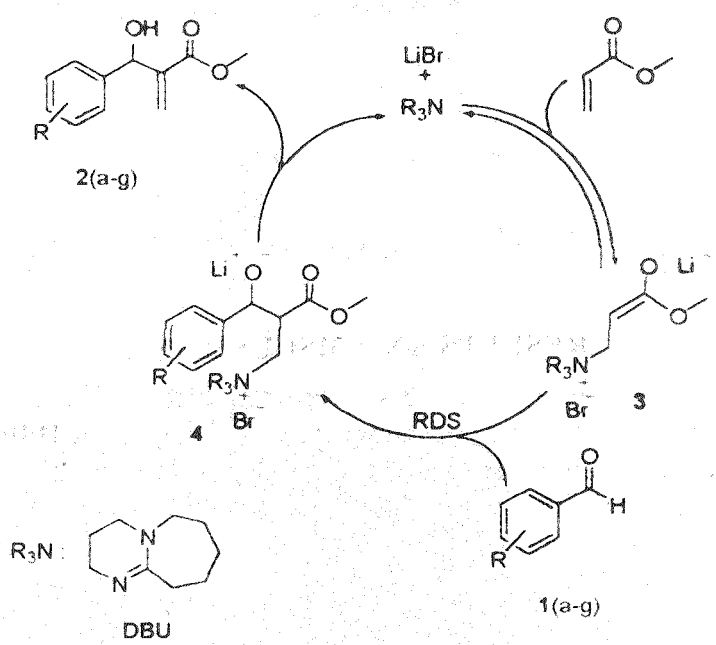


Scheme-1

A proposed mechanism of Baylis-Hillman reaction is shown in **Scheme-2.** Mechanistic studies of this reaction show[1c] that the rate-determining step (RDS) of this reaction is the reaction of the aldehyde **1** with the ammonium enolate **3.** This enolate is formed by conjugate addition of the nucleophilic amine (DBU) to the methyl acrylate (a reversible process) and therefore to obtain faster rates, higher concentration of the enolate and stabilization of ammounium enolate **3** as intermediate are required. DBU is a useful amine which can shift the equilibrium towards the generation of higher concentration of the enolate **3** by stabilizing this species and increases its equilibrium concentration and finally results in significant rate enhancement.[10]

Since DBU plays an important role in this process, the metal salt and DBU have to work independently[12]. We searched for metal salts that work efficiently even in the presence of a tertiary amine. After testing several metal salts, it was found that the Baylis-Hillman reaction is accelerated by using LiBr as co-catalyst.

We found that LiBr is a very effective co-catalyst and the best yield was obtained when 1.0 equiv. of LiBr was used in the presence of 1.0 equiv. of DBU. The reaction sequence involves charged transition states and intermediate **3** that could be stabilized by salt effect to accelerate the reaction rate **(Scheme-2)**. Several aryl aldehyds were tested and the results are summarized in Table-1. In all cases, the reactions proceeded smoothly in the presence of aldehyde (1.0 equiv.), methyl acrylate (1.0 equiv.), LiBr (1.0 equiv.), and DBU (1.0 equiv.), to afford the corresponding adducts in high yields (84–94%) at –10°C to room temperature.



Scheme-2

TABLE-1
EFFECT OF LiBr ON THE TIME AND YIELD OF THE BAYLIS-HILLMAN REACTIONS

Entry	Aldehyde (1)	Co-catalyst[a]	Time (h)	Yield[b, c] (%)
a	Benzaldehyde	none	6	89[10, d]
		LiBr	3.5	94
b	3-Pyridinecarbaldehyde	none	7	85
		LiBr	4.5	93
c	2-Chlorobenzaldehyde	none	10	84
		LiBr	5	90
d	4-Chlorobenzaldehyde	none	8	85[d]
		LiBr	4	92
e	2-Chloro-6-fluorobenzaldehyde	none	6	80
		LiBr	3.5	94
f	4-Methylbenzaldehyde	none	30	70[d]
		LiBr	7	84
g	4-Methoxybenzaldehyde	none	48	62[10, d]
		LiBr	8	88

[a]Reaction conducted on 2 mmol scale using 1 equiv. of LiBr.
[b]Products have been fully characterized spectroscopically by ^{1}H NMR, IR, elemental analyses.
[c]Isolated yields.
[d]Products were identified by comparison with authentic samples.

A preliminary kinetic study in the reaction of several aryl aldehydes with methyl acrylate revealed that relative rate of the reaction using LiBr was considerably faster than that of the reaction without LiBr (Table-2). It seems that the origin of the rate acceleration observed with LiBr is dominated by salt effects and stabilizing the ammonium enolate **3**.

TABLE-2
KINETIC STUDIES OF THE BAYLIS-HILLMAN REACTIONS IN THE PRESENCE OF LiBr

Entry	Aldehyde (1)	Rate (% per min)	K_{rel}
a	Benzaldehyde	0.45	1.80
b	3-Pyridinecarbaldehyde	0.35	1.75
c	2-Chlorobenzaldehyde	0.30	2.14
d	4-Chlorobenzaldehyde	0.38	2.14
e	2-Chloro-6-fluorobenzaldehyde	0.45	2.03
f	4-Methylbenzaldehyde	0.20	5.15
g	4-Methoxybenzaldehyde	0.18	8.60

In conclusion, we have found that LiBr as a cheap, safe and very effective co-catalyst accelerates the Baylis-Hillman reaction in a solvent-free reaction.

ACKNOWLEDGEMENT

Financial support for this work by the Research Council of the Guilan University is gratefully acknowledged.

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(*Received*: 14 January 2005; *Accpeted*: 15 November 2005) AJC-4498