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Short communication

$LiOH{\cdot}H_2O$ as a novel dual activation catalyst for highly efficient and easy synthesis of 1,3-diaryl-2-propenones by Claisen–Schmidt condensation under mild conditions

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Abstract

Commercially available $LiOH{\cdot}H_2O$ was found to be a highly efficient dual activation catalyst for Claisen–Schmidt condensation of various aryl methyl ketones with aryl/heteroaryl aldehydes providing an easy synthesis of 1,3-diaryl-2-propenones under mild conditions. The reactions were carried out at room temperature and in short times affording high yields. Excellent chemoselectivity was observed with carbonyl substrates bearing halogen atom and nitro group without any competitive aromatic nucleophilic substitution. The resultant chalcones did not undergo Michael addition with the ketone enolate. The rate of Claisen–Schmidt condensation was found to be dependent on the steric and electronic factors of the carbonyl substrates.

Keywords: Claisen–Schmidt condensation; Aldehydes; Ketones; 1,3-Diaryl-2-propenones; Lithium hydroxide; Dual activation catalyst

1. Introduction

The 1,3-diaryl-2-propenone moiety has earned the status of a privileged pharmacophore as compounds bearing this moiety (chalcones) possess a broad spectrum of biological activity [1]. Recent studies on biological evaluation of chalcones revealed them to be anti-malarial [2–4], anti-cancer [5,6], anti-leishmanial [7,8], anti-inflammatory [9–11], anti-mitotic [12], anti-tuberculosis [13], cardiovascular [14], cell differentiation inducing [15], nitric oxide regulation modulatory [16,17] and anti-hyperglycemic [18] agents. 1,3-Diaryl-2-propenones inhibit various enzymes such as $CysLT_1$ [19], COX/5-LOX [20], EGFR tyrosine kinase [21] and tyrosinase [22] that play crucial role in the biochemical pathways of different diseases. Chalcones are key precursors in the synthesis of a large array of biologically important heterocycles [23–30] and 1,4-diketones [31]. Thus, the synthesis of chalcones has generated vast interest to organic/medicinal chemists. The convenient approach for synthesis of 1,3-diaryl-2-propenones involves Claisen–Schmidt condensation of aryl methyl ketones with aldehydes. The reaction is catalysed by various bases such as NaOH [2–4,11,12,19,22,26,27,32–36], KOH [13,19,20,37,38], $Ba(OH)_2$ [10,39–41], hydrotalcites [42], LiHMDS [43] and calcined $NaNO_3$/natural phosphate [44,45]. The acid-catalysed methodologies include the use of $AlCl_3$ [46], BF_3 [47], dry HCl [48,49], $Zn(bpy)(OAc)_2$ [50], $TiCl_4$ [51], $Cp_2ZrH_2/NiCl_2$ [52], zeolites [42] and $RuCl_3$ [53]. Recently chalcone synthesis has been achieved employing Suzuki reaction [54].

The reported procedures have various disadvantages such as long reaction times (14 h–5 days) [10,13,19,20,37–41,46,48–53], special efforts needed to prepare the catalysts [42,44,45] and starting materials [39,52], high temperatures [42,50,52,53] requirement of special apparatus [40,52], use of costly reagents [39,43,54], etc. The high temperatures and long reaction times required in the reported methodologies led to impure products due to side reactions and necessitated elaborative work up and purification procedures. Thus, there is a need to develop a better method.

Since most of the acid-catalyzed reactions required high temperatures, responsible for generating side products, we focused

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our attention to the base-catalyzed reaction. However, long reaction times were needed for the reported base-catalyzed synthesis of chalcones and became detrimental to purity of the desired product due to side reactions such as degradation [55] and Michael addition [56–58] under basic medium. We felt that the use of catalytic quantities of a base should minimize the side reactions and the activation of the aldehyde carbonyl group by coordination with the metal counter cation help in carrying out the reaction in short times. Earlier we have demonstrated the use of $LiOH{\cdot}H_2O$ for synthesis of aryl methyl ethers [59] and methyl esters [60]. We report herein for the first time $LiOH{\cdot}H_2O$ as a dual activation catalyst for Claisen–Schmidt condensation of aryl methyl ketones with aryl/heteroaryl aldehydes for easy synthesis of 1,3-diaryl-2-propenones under mild conditions.

2. Results and discussion

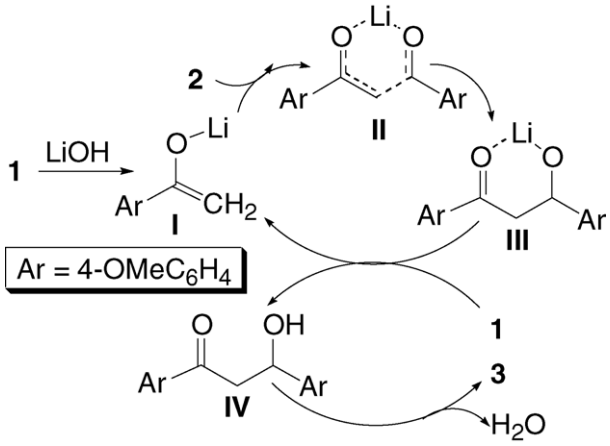
In a model study, we carried out Claisen–Schmidt condensation of 4-methoxyacetophenone (**1**) with 4-methoxybenzaldehyde (**2**) in the presence of $LiOH{\cdot}H_2O$ (10 mol%) and were delighted to observe that a quantitative formation (GCMS) of 4,4′-dimethoxychalcone (**3**) took place after 45 min in EtOH. Use of NaOH, KOH, CsOH, $Mg(OH)_2$, $Ba(OH)_2$, $Ca(OH)_2$ and Me_4NOH under similar conditions afforded poor yields (0–27%) (Table 1). The fact that the use of stronger bases such as NaOH, KOH and CsOH afforded inferior results suggested that $LiOH{\cdot}H_2O$ plays the dual role, i.e. generates the enolate from the aryl methyl ketone and activate the aldehyde carbonyl by coordination with Li^+ (Scheme 1).

Proton abstraction from **1** by $LiOH{\cdot}H_2O$ (present in catalytic amount) generated the lithium enolate **I**. Coordination of the Li^+ cation of **I** with the aldehyde carbonyl oxygen formed the six-membered cyclic transition state **II** and increased the electrophilicity of the aldehyde carbonyl group and made it more susceptible to nucleophile attack in an intramolecular fashion

Table 1
Claisen–Schmidt condensation of **1** with **2** to form **3** under the catalytic influence of various metal hydroxides[a]

Entry	MOH	Solvent	Time (h)	Conversion (%)[b]	Yield (%)[c,d]
1	$LiOH{\cdot}H_2O$	Neat	24	20	15
2	$LiOH{\cdot}H_2O$	EtOH	0.66	100	96
3	NaOH	EtOH	0.66	31	27
4	KOH	EtOH	0.66	5	–
5	$CsOH{\cdot}H_2O$	EtOH	0.66	20	17
6	$Ba(OH)_2{\cdot}8H_2O$	EtOH	0.66	39	36
7	$Ba(OH)_2{\cdot}8H_2O$	EtOH	24	69	60
8	$Ba(OH)_2{\cdot}8H_2O$	Neat	24	Nil	Nil[e]
9	$Ca(OH)_2$	EtOH	24	Nil	Nil
10	$Mg(OH)_2$	EtOH	24	Nil	Nil
11	Me_4NOH	EtOH	24	30	25

[a] The ketone **1** (1 mmol) was treated with the metal hydroxide (10 mol%) in EtOH (0.5 mL) (except for entries 1 and 8) at room temperature for 10 min followed by **2** (1 mmol) for the indicated time at room temperature.
[b] Determined by GCMS.
[c] Isolated yield of **3** obtained after purification by recrystallization.
[d] The product was characterized by IR, ^1H and ^{13}C NMR and MS.
[e] GCMS indicated 8% conversion to **3** after 24 at 100 °C.



Scheme 1. LiOH-catalyzed Claisen–Schmidt reaction.

to form the aldolate anion **III**. The aldolate anion subsequently abstracted the α-proton of **1** and generated the enolate **I** to complete the catalytic cycle. The aldol **IV** on dehydration resulted in the formation of **3**.

To establish generality, Claisen–Schmidt condensation of various aryl methyl ketones with different aromatic and heteroaromatic aldehydes was carried out in the presence of $LiOH{\cdot}H_2O$ (Table 2). Excellent results were obtained in each case. The reactions were carried out in short times (2 min–4 h) and were monitored by GCMS, IR and TLC (in cases where the product formation was very fast, e.g. 2–5 min). We observed that after the completion of the reaction a yellow/orange precipitate appeared and this could be used as indicator for monitoring the reaction visually. The reactions were easy to perform and did not require elaborative work up. The products were isolated by filtration. However, for small-scale reactions (1–2 mmol), in some instances the product recovery was less due to loss during filtration. In general, the reactions were clean and the isolated products were obtained in pure form (IR, NMR and GCMS) without further purification. The chalcone formation took place with excellent chemoselectivity. No competitive side reactions such as product decomposition, aromatic nucleophilic substitution, Michael addition, etc. were observed (GCMS). Substrates with halogen atom (entries 5, 11, 13, 26–29) and nitro group (entries 6, 14, 24, 25) did not experience any aromatic nucleophilic substitution. It has been reported that decomposition of chalcone took place in the presence of KOH [55]. The reaction of acetophenone with 2-pyridylcarboxaldehyde, in ethanolic KOH led to Michael addition of acetophenone enolate to the chalcone and provided the Michael adduct as the final product [56]. Under the present study, exclusive formation of chalcone took place during the reaction of 4-methoxyacetophenone with 2-pyridylcarboxaldehyde (entry 17). The reaction rate was found to be dependent on the steric and electronic factors. The reactions of aldehydes bearing electron-donating groups such as Me, OMe and NMe_2 took longer time than the corresponding reactions of benzaldehyde (compare entry 1 with entries 2–4; entry 9 with entries 10, 12, 15 and 16; entry 27 with entries 28 and 29; entry 31 with entry 34). The presence of electron-withdrawing

Table 2
$LiOH{\cdot}H_2O$-catalysed Claisen–Schmidt reaction of Ar^1COCH_3 with Ar^2CHO[a]

Entry	Ar^1	Ar^2	Time (min)	Yield (%)[b,c,d]
1	C_6H_5	C_6H_5	5	85
2	C_6H_5	4-OMe-C_6H_4	15	88
3	C_6H_5	4-NMe_2-C_6H_4	10	85
4	C_6H_5	4-Me-C_6H_4	30	91
5	C_6H_5	4-Cl-C_6H_4	15	90
6	C_6H_5	4-NO_2-C_6H_4	2	80
7	C_6H_5	1-Naphthyl	25	69
8	C_6H_5	2-Naphthyl	5	91
9	4-OMe-C_6H_4	C_6H_5	15	80
10	4-OMe-C_6H_4	4-Me-C_6H_4	15	72
11	4-OMe-C_6H_4	4-Cl-C_6H_4	30	90
12	4-OMe-C_6H_4	4-OMe-C_6H_4	45	96
13	4-OMe-C_6H_4	4-F-C_6H_4	15	92
14	4-OMe-C_6H_4	4-NO_2-C_6H_4	2	95
15	4-OMe-C_6H_4	3,4-Di-OMe-C_6H_3	180	91
16	4-OMe-C_6H_4	2,4,6-Tri-OMe-C_6H_2	240	82
17	4-OMe-C_6H_4	2-Pyridyl	5	88
18	4-OMe-C_6H_4	3-Pyridyl	3	79
19	4-OMe-C_6H_4	4-Pyridyl	10	70
20	4-OMe-C_6H_4	2-Furyl	4	66
21	4-OMe-C_6H_4	2-Thienyl	5	86
22	4-OMe-C_6H_4	1-Naphthyl	15	87
23	4-OMe-C_6H_4	2-Naphthyl	7	96
24	4-NO_2-C_6H_4	C_6H_5	1	82
25	4-NO_2-C_6H_4	4-OMe-C_6H_4	1	95
26	4-Br-C_6H_4	4-OMe-C_6H_4	60	90
27	4-Cl-C_6H_4	4-OMe-C_6H_4	15	73
28	4-Cl-C_6H_4	3,4-Di-OMe-C_6H_3	180	82
29	4-Cl-C_6H_4	2,4,6-Tri-OMe-C_6H_2	240	80
30	2,4-Di-OBz-C_6H_3	C_6H_5	150	84
31	3,4-Di-OMe-C_6H_3	4-OMe-C_6H_4	60	87
32	3,4-Di-OMe-C_6H_3	2,4,6-Tri-OMe-C_6H_2	180	75
33	3,4-Di-OMe-C_6H_3	3,4,5-Tri-OMe-C_6H_2	240	86
34	3,4,5-Tri-OMe-C_6H_2	4-OMe-C_6H_4	120	88

[a] The ketone in EtOH (0.5–1 mL/mmol) was treated with $LiOH{\cdot}H_2O$ (10 mol%) for 10 min at room temperature followed by the aldehyde (1 equiv.) for the desired period at room temperature.
[b] Isolated yield of the corresponding chalcone.
[c] All of the products were characterized by spectral data (IR, ^1H and ^{13}C NMR and MS).
[d] All new compounds gave satisfactory elemental analysis.

group such as F and NO_2 in the aldehyde allowed the reaction to be carried out in shorter times (compare entry 1 with entry 6; entry 9 with entries 13 and 14). The presence of an electronic-withdrawing group in the aryl methyl ketone accelerated the rate of Claisen–Schmidt condensation presumably because of ease of formation of the corresponding enolate anion (compare entry 1 with entry 24 and entry 2 with entry 25). Comparison of the results of entries 1, 9 and 31 and those of entries 2, 12, 31 and 34 revealed that the presence of electron-donating substituents (e.g. OMe) on the aryl methyl ketone increased the reaction time probably due to sluggishness in proton abstraction from aryl methyl ketones bearing electron-donating groups. The influence of steric factor on the rate of the reaction was exemplified by the results of entries 7 and 8. The peri hydrogen in 1-naphthaldehyde (entry 7) exerted steric hindrance for approach of acetophenone enolate anion towards the aldehyde carbonyl. Similar effect was observed during the reaction of 1- and 2-naphthaldehydes with 4-methoxyacetophenone (entries 22 and 23).

The following representative examples compared the efficiency of the present method with that of the reported procedures. Condensation of benzaldehyde, 4-methoxybenzaldehyde, 4-dimethylaminobenzaldehyde, 4-methylbenzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde with acetophenone afforded 81, 96, 77, 88, 72 and 86% yields, respectively, after 18 h at 80 °C in DMF in the presence of $Zn(bpy)(OAc)_2$ [50]. The corresponding Claisen–Schmidt condensations, catalysed by $LiOH{\cdot}H_2O$, afforded 85, 88, 85, 91, 90 and 80% yields after 5, 15, 10, 30, 15 and 2 min, respectively, at room temperature in EtOH (entries 1–6). The $Zn(bpy)(OAc)_2$-catalysed condensation of 2-pyridylcarboxaldehyde with acetophenone provided 31% chalcone after 16 h at 80 °C in DMF [50] in comparison to 88% yield of the chalcone when 2-pyridylcarboxaldehyde was treated with 4-methoxyacetophenone for 5 min at room temperature in EtOH under the catalytic influence of $LiOH{\cdot}H_2O$ (entry 17). The $Ba(OH)_2$-catalysed reaction of benzoylmethyl-triphenylphsophonium bromide with 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde afforded 20, 36, 49 and 80% yields in 60, 120, 90 and 90 min, respectively, at 70 °C [61]. The corresponding chalcones were obtained in 91, 88, 90, 80% yields in 30, 15, 15 and 2 min, respectively, at room temperature under the present study (entries 4, 2, 5 and 6). The $RuCl_3$-catalysed condensation of acetophenone with benzaldehyde, 4-methylbenzaldehyde and 4-methoxybenzaldehyde afforded the corresponding chalcone in 90, 92 and 94% yields, respectively, after 72 h under heating at 120 °C in sealed glass tubes. Comparable yields of these chalcones were obtained after 5, 30, 15 and 2 min in carrying out the reaction at room temperature under the catalytic influence of $LiOH{\cdot}H_2O$. The reaction of 4-methoxyacetophenone with 4-methoxybenzaldehyde carried out in the presence of calcined $NaNO_3$/natural phosphate for 48 h, afforded 70% yield of the chalcone [44]. Compared to this observation, 96% yield of the chalcone was obtained after 45 min when the corresponding condensation was carried out under the catalytic influence of $LiOH{\cdot}H_2O$. The recently reported Suzuki coupling afforded 81% yield of 3′,4,4′-trimethoxychalcone by the treatment of 3,4-dimethoxybenzoyl chloride (2 equiv.) with 4-methoxyphenylvinylboronic acid (1 equiv.) in the presence of $(PPh_3)_4PPd(0)$ (3 mol%) and Cs_2CO_3 (5 equiv.) in toluene under reflux for 4 h [54]. A 87% yield of 3′,4,4′-trimethoxychalcone was obtained after 1 h at room temperature under the present investigation (entry 31). The reaction of 2,4-di-benzyloxyacetophenone with benzaldehyde (entry 30) exemplified the advantage of the present methodology over the LiHMDS protocol [43]. The desired chalcone was obtained in 40% yield in carrying out the condensation in the presence of stoichiometric amount of LiHMDS at −78 °C for 12 h [43]. In comparison to this, a 90% yield was obtained after 2.5 h at room temperature following the present method.

3. Conclusion

In conclusion, we have described $LiOH{\cdot}H_2O$ as a novel dual activation catalyst for Claisen–Schmidt condensation of aryl methyl ketones with aryl/heteroaryl aldehydes for easy and highly efficient synthesis of 1,3-diaryl-2-propenones under mild conditions. The advantages include (i) the use of cheap, easy to handle and commercially available catalyst, room temperature and non-anhydrous reaction conditions, (ii) short reaction times, (iii) excellent chemoselectivity, (iv) high yields and purity.

4. Experimental

The ^1H and ^{13}C NMR spectra were recorded on Bruker Avance DPX 300 (300 MHz) spectrometer in $CDCl_3$ using TMS as internal standard. The IR spectra were recorded on Nicolet Impact 400 spectrometer as KBr pellets for solid and neat for liquid samples. The reactions were monitored by TLC (silica gel-G) and Shimadzu QP 5000 GCMS. Evaporation of solvents was performed at reduced pressure, using a Büchi rotary evaporator.

4.1. Typical procedure for Claisen–Schmidt condensation

4-Methoxyacetophenone (**1**) (150 mg, 1 mmol) in EtOH (0.5 mL) was treated with $LiOH{\cdot}H_2O$ (4 mg, 0.1 mmol, 10 mol%) under magnetically stirred condition for 10 min at room temperature (~25–30 °C) followed by 4-methoxybenzaldehyde (**2**) (136 mg, 1 mmol, 1 equiv.). The mixture was stirred magnetically until complete consumption of the starting materials (35 min, GCMS). After the completion of the reaction, a yellow precipitate was formed and this served as indicator for monitoring the reaction visually. EtOH was removed under reduced pressure. The residue was diluted with water (5 mL), neutralized with 2% aqueous HCl and extracted with EtOAc (3× 5 mL). The combined EtOAc extracts were washed with brine solution (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford **3** (257 mg, 96%) (Table 2, entry 12).

The remaining reactions were carried out following this general procedure. The isolated products were obtained in pure form (IR, NMR, MS) and did not require further purification. Wherever necessary purification was achieved by crystallization (EtOH) or passing through a column of silica gel (60–120 mesh) and eluting with 1:10 EtOAc–hexane. For large-scale synthesis, the products were isolated by filtration. Typically, the large-scale reactions were performed as follows. Treatment of **1** (1.5 g, 10 mmol) in EtOH (10 mL) with $LiOH{\cdot}H_2O$ (42 mg, 1 mmol, 10 mol%) followed by **2** (1.36 g, 10 mmol, 1 equiv.) resulted a yellow precipitate. The mixture was diluted with ice-cold 1% aqueous HCl (15 mL), filtered, washed with brine (2× 5 mL) and air-dried to afford **3** (2.57 g, 96%). For nitrogen-containing products, water was used in place of 1% aqueous HCl.

4.2. Spectral data of respresentative compound (entry 12, Table 2)

IR (KBr) cm^{-1}: 2932, 1655, 1592, 1566, 1508, 1253, 1165, 1014, 983, 810; ^1H NMR (300 MHz, $CDCl_3$): 8.03 (d, 2H, J = 8.7 Hz), 7.78 (d, 1H, J = 15.5 Hz), 7.60 (d, 2H, J = 8.6 Hz), 7.43 (d, 1H, J = 15.5 Hz), 6.98 (d, 2H, J = 8.8 Hz), 6.93 (d, 2H, J = 8.6 Hz), 3.88 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 188.6, 163.2, 161.4, 143.7, 131.3, 130.6, 130.0, 127.7, 115.5, 114.3, 113.7, 55.4, 55.3; MS (EI) m/z: 268 (M^+) identical with an authentic sample of **3** [44].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2005.08.039.

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