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Short communication

Dual-activation protocol for tandem cross-aldol condensation: An easy and highly efficient synthesis of α,α′-bis(aryl/alkylmethylidene)ketones

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Abstract

Commercially available lithium hydroxide monohydrate ($LiOH{\cdot}H_2O$) was found to be a novel 'dual activation' catalyst for tandem cross-aldol condensation between cyclic/acyclic ketones and aromatic/heteroaromatic/styryl/alkyl aldehydes leading to an efficient and easy synthesis of α,α′-bis(aryl/alkylmethylidene)ketones at r.t. in short times. The reaction of aryl, heteroaryl, styryl and alkyl aldehydes with acyclic and five/six-membered cyclic ketones afforded excellent yields after 2 min to 1.25 h. The reaction conditions were compatible with various electron withdrawing and electron donating substituents, e.g. Cl, F, NO_2, OMe and NMe_2. The rate of the cross-aldol condensation was influenced by the nature of the ketone and electronic and steric factors associated with the aldehyde. The reaction took place at a faster rate for acyclic ketone (e.g., acetone) than that for cyclic ketone (e.g., cyclohexanone). In case of cycloalkanones, the rate of the reaction was dependent on the size of the ring of the cycloalkanone. The cross-aldol condensation of cyclopentanone was faster than that of cyclohexanone for a common aldehyde. In case of reactions involving aliphatic aldehyde having α-hydrogen atom no self-aldol condensation of the aldehyde took place.

Keywords: Dual-activation; $LiOH{\cdot}H_2O$; Catalyst; Tandem cross-aldol; Ketones; Aldehydes; α,α′-bis(aryl/alkylmethylidene)ketones

1. Introduction

The bis(arylmethylidene)cycloalkanone moiety is a novel and versatile pharmacophore as compounds bearing this structural unit possess a broad spectrum of biological activities such as HIV-1 integrase inhibitory [1,2], cytotoxic [3,4], cancer chemopreventive [5] and anti-oxidant [6] properties. The bis(arylmethylidene)cycloalkanones are key starting materials for synthesis of a new class of spiro pyrrolidines as antimicrobial and antifungal agents [7], tricyclic thiazolo[3,2-*a*]thiapyrano[4,3-*d*]pyrimidines and related analogues as potential anti-inflammatory agents [8] and other bioactive and novel heterocycles [9,10]. Thus, the synthesis of bis(arylmethylidene)cycloalkanones has attracted the attention of synthetic organic/medicinal chemists. The general approach involves cross-aldol condensation of a cycloalkanone with an aromatic aldehyde [11], commonly catalysed by a base [12] or an acid [13], (Scheme 1). Subsequently improved methodologies have been reported that used various reagents/Lewis acids such as $(EtO)_4Si/CsF$ or KF [14], Cp_2ZrH_2–$NiCl_2$ [15], Rh(III)-porphyrin [16], Cp_2TiPh_2 [17], BMPTO under microwave irradiation [18], $RuCl_3$ [19], $TiCl_3OTf$ [20], $FeCl_3$-[bmim][BF_4] [21,22], SmI_3[23], KF-Al_2O_3 under ultrasound irradiation [24], TMSCl-NaI [25], H_2SO_4-SiO_2 [26], $Yb(OTf)_3$ [27], Et_2NTMS-LPDE [28], and $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ under microwave irradiation [29]. However, one or more of the disadvantages such as the use of costly catalysts, use of hazardous agents (nickel compounds are toxic, perchlorates are potentially explosive, silica sulfuric acid is corrosive etc.), use of stoichiometric amounts of the catalyst, need to use special apparatus, special efforts required for catalyst preparation (KF-Al_2O_3, silica sulfuric acid, etc.), stringent reaction conditions (e.g., high temperature, sealed tube heating, etc.), long reaction times, moderate yields, etc. encountered with the reported procedures necessitates the development of a more efficient procedure.

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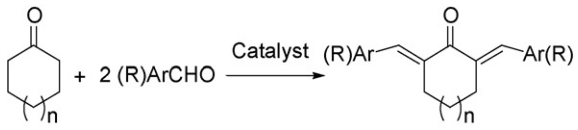


Scheme 1. Tandem cross-aldol condensation for synthesis of α,α′-bis(aryl/alkylmethylidene)cycloalkanones.

In the course of our studies on the application of $LiOH{\cdot}H_2O$ as a cheap and easily available reagent in organic reactions we have found that it acts as a 'dual activation' agent for chemoselective methyl ether [30] and methyl ester [31] formation providing an alternating method to the toxic diazomethane protocol. Recently we reported that $LiOH{\cdot}H_2O$ catalysed the Claisen–Schmidt condensation between aromatic ketones and aromatic/heteroaromatic aldehydes leading to the formation of 1,3-diarylpropenones [32]. We report herein that $LiOH{\cdot}H_2O$ acts as a 'dual activation' catalyst for tandem cross-aldol condensation between acyclic/cyclic ketones and aromatic/heteroaromatic/styryl/alkyl aldehydes leading to an easy and highly efficient synthesis of α,α′-bis(aryl/alkylmethylidene)ketones under mild conditions.

2. Results and discussion

To find out the efficiency of $LiOH{\cdot}H_2O$ as a 'dual activation' catalyst for tandem cross-aldol condensation, we planned to carry out the model study using a less electrophilic aromatic aldehyde. Since the first step of the cross-aldol condensation involves nucleophilic attack of the ketone enolate on the carbonyl carbon of the aldehyde, we thought that a less electrophilic aldehyde should be the ideal choice for a model substrate. Thus, cyclohexanone (**1**) (1 mmol) was treated with 3,4,5-trimethoxybenzaldehyde (**2**) (2 equiv.) in the presence of $LiOH{\cdot}H_2O$ (10 mol%) in EtOH (1.5 mL). We were delighted to observe that formation of 2,6-bis(3′,4′,5′-trimethoxybenzylidine)cyclohexanone (**3**) took place in 80% (NMR) yield after 60 min in EtOH. Use of other metal hydroxides such as NaOH, KOH, $CsOH{\cdot}H_2O$, $RbOH{\cdot}H_2O$, $Mg(OH)_2$, $Ba(OH)_2$ and $Ln(OH)_3{\cdot}H_2O$ under similar conditions did not afford significant amount of **3** (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 ketone and activates the aldehyde carbonyl by coordination with Li^+ (Scheme 2). The reaction was best carried out by addition of **2** to the magnetically stirred mixture of $LiOH{\cdot}H_2O$ and **1**. When the reaction was carried out by mixing **1**, **2** and $LiOH{\cdot}H_2O$ simultaneously, longer time was required for completion of the reaction.

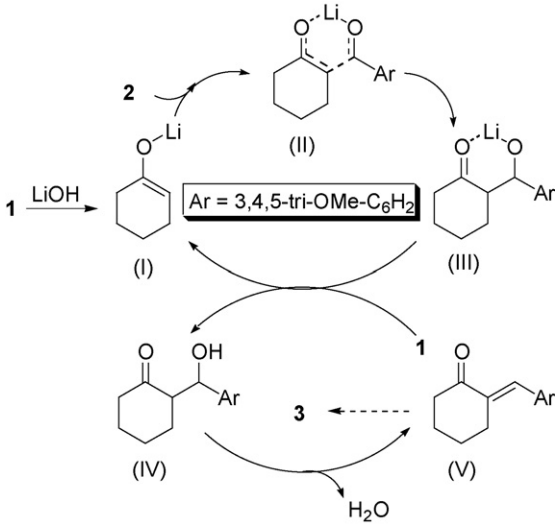
The need to use $LiOH{\cdot}H_2O$ was revealed by the fact that the use of other metal hydroxides failed to produce significant amount of the desired product. No cross-aldol condensation was observed when **1** was treated with **2** in the absence of $LiOH{\cdot}H_2O$ either in the presence or absence of solvent (Table 1, entries 10 and 11). The inferior result obtained in carrying out the reaction under neat conditions (Table 1, entry 2) was due to incomplete conversion as the reactants were trapped by the solid cross-aldol condensation product.

Table 1
Cross-aldol condensation between **1** and **2** in the presence of various metal hydroxides[a]

Entry	Base	Yield (%)[b]
1	$LiOH{\cdot}H_2O$	80
2	$LiOH{\cdot}H_2O$	60[c]
3	NaOH	Nil
4	KOH	Trace
5	$RbOH{\cdot}H_2O$	Nil
6	$CsOH{\cdot}H_2O$	Trace
7	$Mg(OH)_2$	Nil
8	$Ba(OH)_2$	Nil
9	$La(OH)_3{\cdot}H_2O$	Nil
10	None	Nil
11	None	Nil[c]

[a] **2** (2 mmol) was added to the magnetically stirred mixture of **1** (1 mmol) and the metal hydroxide (10 mol%) (except for entries 10 and 11) in EtOH (1.5 mL) (except for entries 2 and 11) at r.t. (∼25–30 °C) for 1 h.
[b] Yield of **3** calculated on the basis of ^{1}H NMR (300 MHz).
[c] The reaction was carried out in the absence of solvent.

The role of $LiOH{\cdot}H_2O$ is demonstrated in Scheme 2. Proton abstraction from **1** by $LiOH{\cdot}H_2O$ (present in catalytic amount) generates the lithium enolate **I**. Coordination of the Li^+ cation of **I** with the aldehyde carbonyl oxygen forms the six-membered cyclic transition state **II** and increases the electrophilicity of the aldehyde carbonyl group and makes it more susceptible to nucleophilic attack in an intramolecular fashion to form the aldolate anion **III**. The aldolate anion subsequently abstracts the α-proton of **1** and generates the enolate **I** to complete the catalytic cycle. The aldol **IV** on dehydration results in the formation of arylidinecyclohexanone **V** which undergoes a similar sequence of events as experienced by **1** (e.g., proton abstraction to form the enolate, condensation with **2** via a six-membered cyclic transition state mediated through Li-coordination to form the corresponding aldolate anion, proton exchange of the aldolate



Scheme 2. Dual activation role of LiOH during tandem cross-aldol condensation between a ketone and an aldehyde.

Table 2
LiOH·H_2O-catalysed tandem cross-aldol reaction of different ketones with various aldehydes[a]

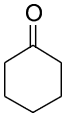
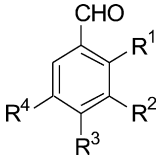
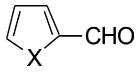
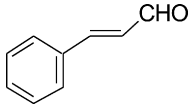
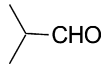
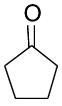
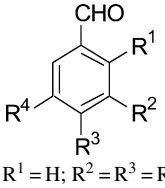
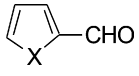
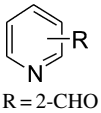
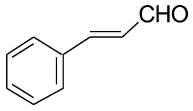
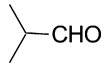
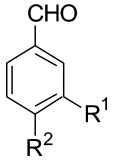
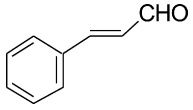
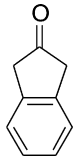
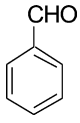
Entry	Ketone	Aldehyde	Time (min)	Yield (%)[b,c]
				
1		$R^1 = H$; $R^2 = R^3 = R^4 = OMe$	60	75
2		$R^1 = R^2 = R^4 = H$; $R^3 = OMe$	45	93
3		$R^1 = R^2 = R^4 = H$; $R^3 = NMe_2$	75	80
4		$R^1 = R^2 = R^3 = R^4 = H$	35	95
5		$R^1 = R^2 = R^4 = H$; $R^3 = Cl$	60	80
6		$R^1 = Cl$; $R^2 = R^3 = R^4 = H$	10	85
7		$R^1 = R^2 = R^4 = H$; $R^3 = NO_2$	10	95
8		$R^1 = R^3 = R^4 = H$; $R^2 = NO_2$	15	84
9		$R^1 = R^2 = R^4 = H$; $R^3 = F$	60	95
				
10		X = S	30	97
11		X = O	30	88
				
12		R = 2-CHO	60	98
13		R = 3-CHO	30	75
14		R = 4-CHO	15	95
15			20	95
16			60	80
				
17		$R^1 = H$; $R^2 = R^3 = R^4 = OMe$	10	96
18		$R^1 = R^2 = R^4 = H$; $R^3 = OMe$	5	96
19		$R^1 = R^2 = R^4 = H$; $R^3 = NMe_2$	25	90
20		$R^1 = R^2 = R^3 = R^4 = H$	2	96
21		$R^1 = R^2 = R^4 = H$; $R^3 = Cl$	10	99
22		$R^1 = Cl$; $R^2 = R^3 = R^4 = H$	2	99
23		$R^1 = R^2 = R^4 = H$; $R^3 = NO_2$	5	98
24		$R^1 = R^3 = R^4 = H$; $R^2 = NO_2$	10	91
25		$R^1 = R^2 = R^4 = H$; $R^3 = F$	20	96
				
26		X = S	2	98
27		X = O	10	89
				
28		R = 2-CHO	15	98
29		R = 3-CHO	5	98
30		R = 4-CHO	2	96

Table 2 (*Continued*)

Entry	Ketone	Aldehyde	Time (min)	Yield (%)[b,c]
31			5	98
32			15	90
				
33		$R^1 = R^2 = H$	5	89
34		$R^1 = H$; $R^2 = OMe$	10	80
35		$R^1 = H$; $R^2 = Cl$	10	91
36		$R^1 = NO_2$; $R^2 = H$	5	90
37			5	91
38			30	85

[a] The aldehyde (2 mmol) was added to the magnetically stirred mixture of the ketone (1 mmol) and LiOH·H_2O (10 mol%) in EtOH (1.5 mL) at r.t. (~25–30 °C).
[b] Isolated yield of bis(aryl/alkylmethylidene)ketones.
[c] The products were characterized by IR, NMR, and MS.

with **V** followed by dehydration of the resultant aldol) to lead to **3**.

To establish the generality, different cyclic and acyclic ketones such as cyclohexanone, cyclopentanone, acetone and 2-indanone were treated with various aryl, heteroaryl, styryl and alkyl aldehydes under the catalytic influence of LiOH·H_2O (10 mol%) (Table 2). Excellent results (75–98% yields) were obtained and the reactions were completed after 2 min to 1.25 h (TLC). The reactions could be monitored visually as the products were highly conjugated carbonyl compounds and were yellow/light orange in colour and precipitated out in the reaction medium due to poor solubility in EtOH at room temperature. Thus, the formation of a yellow or light orange precipitate indicated completion of the reaction. The reaction conditions were compatible with various substituents such as Cl, F, NO_2, OMe and NMe_2. For condensation with a common aldehyde, the reactions of acetone were faster than those of cyclohexanone (compare entries 33–36 with entries 2, 4, 5 and 8; Table 2). Comparison of the results of entries 1–16 (Table 2) with those of entries 17–32 (Table 2) revealed that the reaction of cyclopentanone with a particular aldehyde was faster than that of cyclohexanone with the same aldehyde. This may be due to the removal of the eclipsing effect of the adjacent hydrogen atoms in cyclopentanone after the formation of the arylmethylidene derivative [33]. Aldehydes with electron donating substituent

required longer times due to the decrease in electrophilicity of the aldehyde carbonyl carbon compared to that in substrates devoid of such substituents (compare entry 4 with entries 3 and 5 and entry 20 with entries 19 and 21, Table 2). The faster rate of reaction of 4-NO_2-benzaldehyde compared to that of benzaldehyde (compare entry 4 with 7 and entry 20 with 23, Table 2) was due to the increase in the electrophilic property of the aldehyde carbonyl group in the former due to the electron withdrawing effect of the 4-NO_2 group. The effect of electronic factor of the aldehyde on the rate of reaction was further demonstrated by the reactions of cyclohexanone and cyclopentanone with heteroaryl aldehydes (e.g., 2-thienyl, 2-furyl and pyridyl carboxaldehydes). The longer times required during the condensation of cycloalkanones with 2-pyridyl carboxaldehyde compared to those with 2-thienyl and 2-furyl carboxaldehydes (compare the results of entries 10–12 and those of entries 26–28) were due to the less electrophilic property of the aldehyde carbonyl in the pyridine analogue. The lone pair of electrons of the nitrogen atom in 2-pyridyl carboxaldehyde experienced electrostatic repulsion with the lone pairs of electrons of the oxygen atom of the aldehyde carbonyl group and reduced the electrophilicity of the aldehyde carbonyl carbon. In case of 2-thienyl and 2-furyl carboxaldehydes such type of electrostatic repulsion involving the lone pair of electrons of the sulfur/oxygen atom of the thiophene/furan ring and the lone pair of electrons of the carbonyl oxygen was less likely as the lone pair of electrons of the sulfur/oxygen atom of the thiophene/furan ring were involved to provide aromaticity to the thiophene/furan ring. Thus the carbonyl carbon of 2-thienyl and 2-furyl carboxaldehydes are more electrophilic compared to that of the 2-pyridyl carboxaldehyde. The slower rate of reaction of 2-furyl carboxaldehyde with cyclopentanone compared to that of 2-thenyl carboxaldehyde (compare entries 26 and 27, Table 2) was due to the better electrophility of the aldehyde carbonyl group in 2-thienyl carboxaldehyde as the lone pair of electrons of the sulfur atom of the thiophene ring were more involved in attributing aromatic character of the thiophene ring compared to the lone pair of electrons of the oxygen atom of the furan ring in 2-furyl carboxaldehyde. The role of the electrostatic repulsion involving the lone pair of electrons of the ring nitrogen atom and those of the oxygen atom of the aldehyde carbonyl in reducing the electrophilicity of the carbonyl carbon was further evidenced by the faster rate of reaction with 3- and 4-pyridyl carboxaldehydes (compare the results of entries 12–14 and the results of entries 28–30, Table 2). The faster rate of reaction with 2-chlorobenzaldehyde compared to that of 4-chlorobenzaldehyde (compare entry 5 with 6 and entry 21 with 22, Table 2) further demonstrated the importance of coordination effect involving the Li^+ counter cation of the cycloalkanone enolate. The chelation effect of the aldehyde carbonyl and the *ortho*-Cl groups brings the cycloalkanone enolate in close proximity to the aldehyde carbonyl of the 2-chlorobenzaldehyde and increased the rate of condensation. The shorter reaction time required for *trans*-cinnamaldehyde compared to that of benzaldehyde (compare entry 4 with 15 and entry 20 with 31, Table 2) was due to the reduced steric factor surrounding aldehyde carbonyl carbon in the case of former substrate. The reaction of benzaldehyde with cyclopentanone (entry 20, Table 2) and 2-indanone (entry 38, Table 2) revealed the influence of steric factor of the ketone on the rate of cross-aldol condensation. In case of reactions involving aliphatic aldehyde having α-hydogen atom, the desired α,α′-bis(alkylmethylidene)cycloalkanones were obtained in excellent yields (entries 16 and 32, Table 2) indicating that no significant amount of competitive self-condensation of the aldehyde took place. This further demonstrated the chemoselectivity.

The advantage of the present methodology can be demonstrated by comparing the results of a few representative reactions of cyclohexanone and cyclopentanone with electron rich and electron deficient aldehydes and styryl aldehyde with a few recently reported procedures. The reaction of cyclohexanone and cyclopentanone with 4-methoxybenzaldehyde in the presence of $LiOH{\cdot}H_2O$ (10 mol%) at r.t. afforded 2,6-bis(4-methoxypheylmethylidene)cyclohexanone and 2,5-bis(4-methoxypheylmethylidene)cyclopentanone in 93 and 96% yields after 45 and 5 min, respectively. The corresponding products were obtained in 89 and 95% yields after 3 and 2 h, respectively, under heating at 80 °C in a sealed tube in the presence of silica sulfuric acid (1 equiv.) [26]. The use of costly $Yb(OTf)_3$ (0.5 mol%) provided comparable yields after heating the reaction mixtures at 90 °C for 6 h [27]. A 65% yield of 2,6-bis(4-methoxypheylmethylidene)cyclohexanone was obtained in carrying out the cross-aldol condensation in the presence of $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ (10 mol%) in THF at 60 °C for 24 h and 88% yield was obtained in carrying out the reaction in Schlenk flask fitted with Teflon stopper under microwave irradiation [29]. Cross-aldol condensation of 4-nitrobenzaldehyde with cyclohexanone and cyclopentanone catalysed by $LiOH{\cdot}H_2O$ (10 mol%) afforded the corresponding products in 95 and 98% yields after 10 and 5 min, respectively, at r.t. Compared to these observations, 86 and 92% yields were obtained after 3.5 and 3 h, respectively, on heating the reaction mixtures in the presence of silica sulfuric acid (1 equiv.) in a sealed tube at 80 °C [26]. The $Yb(OTf)_3$ catalysed reactions took 12 h to afford comparable yields on heating at 90 °C [28]. The cross-aldol condensation of *trans*-cinnamaldehyde with cyclohexanone and cyclopentanone afforded 95 and 98% yields after 20 and 5 min, respectively, in the presence of $LiOH{\cdot}H_2O$ (10 mol%) at r.t. The corresponding products were obtained in 86 and 95% yields after 3.5 and 2 h, respectively, in carrying out the reactions by heating the reaction mixtures in a sealed tube at 80 °C in the presence of silica sulfuric acid [26]. Comparable yields were obtained after 6 h at 90 °C during the $Yb(OTf)_3$ catalysed reactions [27]. The $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ (10 mol%) catalysed reactions afforded 78 and 76% yields, respectively, on heating in a closed Schlenk flask for 18 h at 60 °C in THF and 94 and 82% yields could be obtained under microwave heating. Thus, the present protocol is better than the reported methods in terms of ease of carrying out the reaction, cost of catalyst, reaction time, reaction temperature and product yields.

After the completion of this work an amine-catalysed aldol condensation in the presence of $LiClO_4$ has been reported [34]. Although the combined use of a base and a Lewis acid serves the purpose of nucleophile–electrophile dual activation, the present

method demonstrates the first example of the use of a single agent for dual activation catalyst. The requirement of the use of excess (200 mol%) of $LiClO_4$ in this recent report [34] as compared to the use of 10 mol% of $LiOH{\cdot}H_2O$ under the present investigation underlines the significant advantage of this newly developed procedure. The superiority of the present methodology over this report can be demonstrated by the following representative examples. The cross-aldol condensation between cyclopentanone and 3,4-dimethoxybenzaldehyde afforded the desired product in 100% yield after 4 d in the presence of Et_3N (20 mol%) and $LiClO_4$ (200 mol%) whereas reaction of cyclopentanone with 3,4,5-trimethoxybenzaldehyde afforded the corresponding cross-aldol condensation product in 96% yield after 10 min in the presence of 10 mol% of $LiOH{\cdot}H_2O$. The reaction of cyclopentanone with isobutyraldehyde catalysed by Et_3N (20 mol%) and $LiClO_4$ (200 mol%) afforded the 2,5-bis-isobytylidenecyclopentanone in 100% yield after 4 d in comparison to a 90% yield obtained after 15 min during the $LiOH{\cdot}H_2O$ (10 mol%) catalysed reaction.

3. Conclusion

In conclusion, we have discovered $LiOH{\cdot}H_2O$ as a novel dual activation catalyst for tandem cross-aldol condensation of acyclic and cyclic ketones with aryl, heteroaryl, styryl and alkyl aldehydes for an easy and highly efficient synthesis of bis(aryl/alkylmethylidene)ketones. The advantages are (i) use of cheap and easily available catalyst, (ii) requirement of small amount (10 mol%) of the catalyst, (iii) room temperature reaction, (iv) short reaction times, (iv) high product yields and (v) clean product.

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 experimental procedure for synthesis of 2,6-bis-(3′,4′,5′-trimethoxybenzylidene)cyclohexanone (3)

Cyclohexanone (**1**) (98 mg, 1 mmol) in EtOH (1.5 mL) was treated with $LiOH{\cdot}H_2O$ (4 mg, 0.1 mmol, 10 mol%) under magnetically stirred condition for 10 min at r.t. (∼25–30 °C) followed by 3,4,5-trimethoxyabenzaldehyde (**2**) (393 mg, 2 mmol, 2 equiv.). The mixture was stirred magnetically at r.t. until maximum consumption of the aldehyde (30 min, TLC). 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) 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. The crude yellow solid on crystallization (EtOAc-EtOH) afforded **3** (341 mg, 75%). mp: 197 °C.

4.2. Large scale synthesis of 2,6-bis-(3′,4′,5′-trimethoxybenzylidene)cyclohexanone (3)

Treatment of **1** (0.98 g, 10 mmol) with **2** (3.93 g, 20 mmol, 2 equiv.) in EtOH (15 mL) in the presence of $LiOH{\cdot}H_2O$ (42 mg, 1 mmol, 10 mol%) under magnetically stirred condition for 10 min at r.t. (∼25–30 °C) following the above mentioned procedure afforded an yellow solid (3.32 g) after usual work-up. The crude product on crystallization (EtOAc-EtOH) afforded **3** (3.22 g, 71%)

4.3. Spectral data of representative compound (3)

IR (KBr) cm^{-1}: 1659.4; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.8 (d, 2H, $J = 5.5$ Hz), 2.9 (t, 4H), 3.9 (s, 18H), 6.7 (s, 4H), 7.7 (s, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 23.5, 28.9, 56.7, 61.2, 108.4, 131.9, 135.9, 137.6, 139.2, 153.5, 190.4; MS (MALDI-TOF): $m/z = 454$ (M^+) identical with those of an authentic sample [35].

The spectral data (IR, NMR and MS) of all known products were identical with those of authentic compounds. The following compounds were unknown.

2,6-Bis-isobutylidene-cyclohexanone (entry 16; Table 2). IR (neat) cm^{-1}: 2960, 2968, 1681, 1626, 1600, 1463, 1299, 1257, 1169,1139, 901,741; ^1H NMR ($CDCl_3$, 300 MHz): 6.62 (d, 2H, $J = 9.8$ Hz), 2.50–2.54 (t, 4H, $J = 6$ Hz), 1.70–1.78 (m, 2H), 1.01(d, 12H, $J = 7.8$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 191.29$, 147.97, 124.88, 28.41, 27.32, 23.72, 23.04; MS (APCI): $m/z = 206$ (M^+).

2,5-Bis-(3′,4′,5′-trimethoxybenzylidene)cyclopentanone (entry 17; Table 2). mp: 207–208 °C; IR (KBr) cm^{-1}: 1692; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.12 (s, 4H), 3.90 (s, 18H), 6.8 (s, 4H), 7.4 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 26.9, 56.6, 61.5, 108.6, 131.8, 134.5, 136.8, 140.0, 153.7, 196.3; MS (MALDI-TOF): $m/z = 441$ (MH^+).

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