

A Highly Efficient Method for Synthesis of Bisarylmethylidenes of Cyclic Ketones in [BMIm]Cl/NaOH System as New and Recyclable Catalyst

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ABSTRACT

An ionic liquid 1-Butyl-3-methylimidazoliumchloride[BMIm]Cl/sodium hydroxide system, was employed as a catalyst for the fast and one-pot crossed aldol-condensation of various aromatic aldehydes and cyclic ketones, to produce a variety of substituted α,α' -bis(benzylidene)-cycloalkanones under neat conditions. This process is simple, efficient and environmentally benign and proceeds in high yield and short reaction times. The ionic liquid can be recycled for subsequent reactions without any appreciable loss of efficiency.

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1. Introduction

The aldol condensation and related reactions have been widely applied for carbon-carbon bond formation in organic synthesis. Among them, the Claisen–Schmidt condensation of aryl aldehydes with cycloalkanones is an important reaction for the preparation of α,α' -bis(arylidene)cycloalkanones. These arylidene derivatives are intermediates of various pharmaceuticals with intriguing biological activities such as antibacterial and antifungal¹, antitubercular², cytotoxicity³, antioxidant⁴, anti-inflammatory^{4b,5}, antianiogenic⁶, HIV-1 integrase inhibitory⁷, analgesic^{4b, 5b, 8}, antiparkinsonian and anticonvulsant⁸. Moreover, they are used as precursor for agrochemical and perfumes⁹, new organic material for nonlinear optical applications¹⁰, the units of liquid crystalline polymers¹¹, and enantioselective catalysts in the synthesis of medicinally relevant compounds¹².

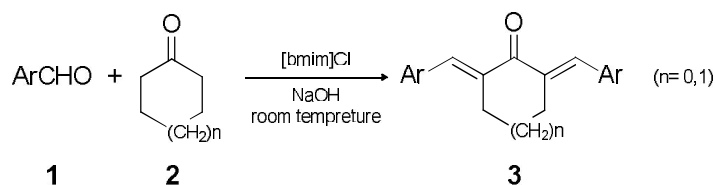
Usually this type of condensation has been catalyzed by bases and occasionally by strong acids. Nevertheless, in such harsh conditions, the reactions suffer from reverse and/or side reactions and

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may give the corresponding products in low yields¹³. Subsequently, improved by utilization of gentle catalysts methodologies have been reported. The most successful catalyst used there was: different organometallic complexes¹⁴, Rh (III) porphyrine¹⁵, RuCl₃¹⁶, SmI₃¹⁷, BF₃·Et₂O¹⁸, FeCl₃·6H₂O¹⁹, ZnBr₂/Et₃N²⁰, Mg(HSO₄)₂²¹, Pd/C-(TMSCl)²², LiClO₄²³, Yb(OTf)₃²⁴, rare earth(III) perfluorooctane sulfonates²⁵, InCl₃·4H₂O²⁶, Cu(OTf)₂²⁷, Cp₂ZrH₂ and Cp₂Zr(O-*i*-Pr)₂²⁸, lithium iodide²⁹, CH₃CO₂Na/CH₃CO₂H³⁰, the micellar medium³¹, polymer-supported sulfonic acid (NKC-9)³², SOCl₂/EtOH³³, TiCl₃(SO₃CF₃)³⁴, Ti(OR)₄³⁵ etc. However, in the most cases, process suffers from high cost and difficult catalyst preparation, uses of toxic or stoichiometric amounts of catalyst, hydrolyzing of catalyst in the presence of water which may result in the aldol-condensation reactions, not recyclability of that catalysts, long reaction time or high reaction temperature, unwanted side reactions, involving complicated or tedious purification operations, generation of large amount of wastes, low yields and peculiar reaction conditions. Therefore, because of the importance for the preparation of α,α' -bis(arylidene)cycloalkanones, it is important to exploit a simple, efficient, and clean procedure for cross-condensation from the views of environmental and green chemistry.

During the past decade, room temperature ionic liquids (RT ILs), have attracted considerable attention due to their special characteristics including high thermal and chemical stability, excellent solubility with organic and inorganic compounds, electrochemical properties, non-flammability, ease of handling and recycling, wide liquid range and negligible vapor pressure. These striking properties allow them to be applied as catalyst and dangerous organic solvent substitutes. Ionic liquids are usually formed by a bulky aromatic organic cation and an inorganic anion. By chemically modifying these two species, ILs can be prepared in large varieties with different, tailor-made properties. Because of all above, ILs have attracted an increasing attention and used in many different applications (chemistry, biochemistry, electrochemistry, or engineering) which is shown in the exponential grown of publications related to these materials³⁶.

Utilization of ionic liquids as catalytic promoter is an important topic in organic synthesis. Following our recent studies on programs aimed at greener chemistry³⁷ we wish to report an efficient, convenient and facile method for the condensation of aldehydes (**1**) with cycloalkanones (**2**) leading to the corresponding α,α' -bis(substitutedbenzylidene)cycloalkanones (**3**) promoted by ionic liquid [BMIm][Cl]/NaOH system (scheme 1).



Scheme 1. Cross-aldol condensation based synthesis of α,α' -bis(benzylidene)cycloalkanones

2. Results and Discussion

Initially, we aimed to examine the possibility of aldol condensation in the presence of [BMIm]OH as a basic ionic liquid, hence we tried to synthesis [BMIm]OH according to the procedure published by Ranu et al³⁸. Surprisingly, we couldn't obtain the desired ionic liquid in pure and stable form. Same result had been observed by Chen et al³⁹. They have founded that [BMIm]OH decomposes rapidly in drying step, but it is moderately stable when a small water content is maintained. These observations led us to in situ generation of [BMIm]OH in aqueous media during the aldol condensation. But before this, we performed a set of experiments to determine and optimize the reaction conditions with several other reagents.

We first chose the reaction of benzaldehyde (2mmol) and cyclohexanone (1 mmol) and several ionic liquids (0.5 mmol) such as 1-butyl-3-methylimidazolium chloride [BMIm]Cl, 1-butyl-3-

methylimidazolium bromide [BMIm]Br, 1-butyl-3-methylimidazolium hexafluorophosphate [BMIm]PF₆ and 1-butyl-3-methylimidazolium tetrafluoroborate [BMIm]BF₄ as a model reaction in water (0.5ml) at ambient temperature. After being stirred for several hours (24 h), the reactants kept unchanged. Increasing temperature had no effect on the course of the reaction.

Based on these results, we then performed the cross-aldol condensation using these ILs in the presence of a base. Interestingly, when NaOH was used as base the corresponding α, α' -bis(benzylidene) cyclohexanone was obtained in good to moderate yields (**Table 1**).

Table 1. Preparation of α, α' -bis(benzylidene)cyclohexanone in several ionic liquids ^a.

Entry	Ionic liquid	Time (h)	Yield (%)
1	[BMIm]Cl	2	88
2	[BMIm]Br	3	85
3	[BMIm]PF ₆	3	43
4	[BMIm]BF ₄	6	56

^a Reaction conditions: 1 mmol ionic liquid, 2 mmol benzaldehyde, 1 mmol cyclohexanone, 1mmol NaOH, 0.5ml water, room temperature.

As can be seen from Table 1, [BMIm]Cl is the suitable choice for an optimum yield. In the next step, a set of experiments were performed to find out the appropriate amount of [BMIm]Cl for this reaction. The results were summarized in Table 2. Best result was obtained when 0.5 mmol of this ionic liquid was used. Excessive amounts of catalyst cannot greatly increase the yields.

Table 2. Effect of the [BMIm]Cl amount on the preparation of α, α' -bis(benzylidene)cyclohexanone ^a

Entry	[BMIm]Cl (mmol)	Yield (%)
1	0.2	60
2	0.5	85
3	1	88

^a Reaction conditions: 2 mmol benzaldehyde, 1 mmol cyclohexanone, 1mmol NaOH, 0.5ml water, room temperature.

In order to study the effect of base type and nature, parallel experiments were carried out using some other organic and inorganic bases (Table 3). As illustrated in Table 3, best results were obtained when Inorganic bases were used. Among organic bases DABCO showed only 45% yield in 48 hours while NaOH gave the yield almost twofold in 2 hours.

Table 3. Effect of base nature on the preparation of α, α' -bis(benzylidene)cyclohexanone ^a

Entry	base	Time (h)	Yield (%)
1	DABCO	48	45
2	Pyrrolidine	48	trace
3	Et ₃ N	48	20
4	K ₂ CO ₃	48	35
5	NaHCO ₃	48	trace
6	KOH	2	87
7	NaOH	2	88

^a Reaction conditions: 1 mmol base, 0.5 mmol [BMIm]Cl, 2 mmol benzaldehyde, 1 mmol cyclopentanone, room temperature

Furthermore, the amount of NaOH in the system was optimized (Table 4).

Table 4. Effect of the NaOH amount on the preparation of α, α' -bis(benzylidene)cyclohexanone ^a

Entry	NaOH (mmol)	Yield (%)
1	0.2	25
2	0.5	62
3	0.75	85
4	1	87


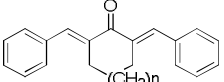
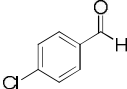
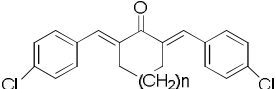
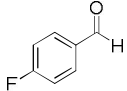
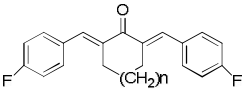
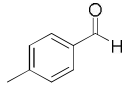
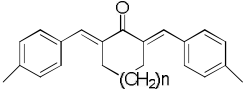
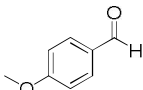
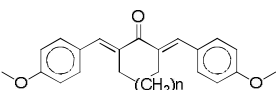
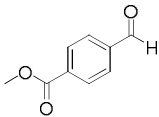
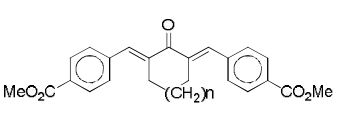

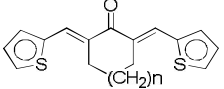

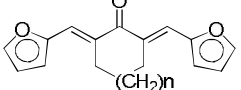
^a Reaction conditions: 0.5 mmol [BMIm]Cl, 2 mmol benzaldehyde, 1 mmol cyclopentanone, 2 hours, room temperature

According to obtained results, we conclude that 0.5 mmol (0.084 g) [BMIm]Cl and 0.75 mmol (0.03 g) NaOH are sufficient for satisfactory results. To evaluate the reaction scope and generality of the catalytic system, the reactions of cyclopentanone and cyclohexanone with several aromatic aldehydes were conducted. The results were summarized in Table 5. The aromatic aldehydes with electron-donating substitutions (entries 4 and 5, Table 5) reacted smoothly with cyclohexanone and cyclopentanone as well as electron-withdrawing groups (entries 2 and 3 Table 5) to afford the corresponding α,α' -bis(substituted benzylidene) cycloalkanones in good to excellent yields.

Comparison of the results revealed that the reaction of cyclopentanone with a particular aldehyde (Table 5, entries 1-6, $n=0$) was faster than that of cyclohexanone with the same aldehyde (Table 5, entries 1-6, $n=1$). 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. In addition, aldehydes with electron donating substituent required longer times due to the decrease in electrophilicity of the aldehyde carbonyl carbon, compared to substrates devoid of such substituents (compare entry 2 and 3 with entries 4 and 5, Table 5). Heterocyclic aldehydes react smoothly under the same conditions but in a higher yield (entries 7-8). The melting points of the synthesized compounds are in agreement with the values reported in the literature (Table 5).

Moreover, using [BMIm]Cl/NaOH/water system as the catalyst and reaction medium also made the separation process much easier. For example, with this system, the product can be obtained with high purity through simple filtration and rinsing of the filtrates with a little amount of water. Whereas, some other methods reported in literature suffer from harsh workup procedure.

Table 5. Condensation of various aromatic aldehydes with cyclic Ketones ^a

Entry	Aldehyde	Product	M.p (°C) (reported ¹)	Yield (%)	Time/min
1			5a: $n=0$: 187-188 (188-189) 5i: $n=1$: 114-115 (116-117)	90 85	60 120
2			5b: $n=0$: 224-226 (227-228) 5j: $n=1$: 145-146 (144-145)	92 94	15 45
3			5c: $n=0$: 239-240 (237-239) 5k: $n=1$: 154-155 (157-159)	94 95	10 70
4			5d: $n=0$: 240-241 (244-245) 5l: $n=1$: 165-166 (163-164)	87 88	45 150
5			5e: $n=0$: 211-212 (211-212) 5m: $n=1$: 159-160 (161-163)	89 84	30 180
6			5f: $n=0$: 280-282 5n: $n=1$: 196-198	86 63	45 240
7			5g: $n=0$: 174-175 (176-178) 5o: $n=1$: 140-142 (142-143)	95 96	60 60
8			5h: $n=0$: 161-162 (163-164) 5p: $n=1$: 144-145 (145-146)	96 95	60 60

^a Reaction conditions: 2 mmol aldehyde, 1 mmol Ketone, 0.5 mmol [BMIm]Cl, 0.75 mmol NaOH, 0.5 ml water, room temperature

Next, we also investigated the reusability and the recycling of the ionic liquid [BMIm]Cl, and founded that the catalyst could be easily recovered after completion of the reaction and reused in subsequent reactions. The reaction of benzaldehyde with cyclohexanone at room temperature as a model reaction was again studied. After completion of the reaction, small amount of water was added to the reaction mixture. The solid precipitate was isolated by filtration and washed with 3×5 ml water. The ionic liquid left in the filtrate was dried under vacuum and reused for again for fresh reaction. The activity of the catalyst did not show any significant decrease after 4 runs (Table 6).

Table 6. Reusability study of the catalyst in the model reaction

round	Yield (%)
1	85
2	83
3	83
4	82

3. Conclusions

In this paper, we present an efficient and convenient protocol for the synthesis α,α' -bis(substituted benzylidene)cycloalkanones via cross-aldol condensation between arylaldehydes and cycloalkanones catalyzed by [BMIm]Cl/sodium hydroxide system. The reaction can be carried out in water at room temperature. The main advantages of this method are mild reaction conditions, higher yields, user friendly and green procedure, shorter reaction period and the possibility of catalyst reuse.

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4. Experimental

4.1. Materials and Methods

The progress of the reaction and the purity of compounds were monitored using Merck 0.2 mm silica gel 60 F-254 Al-plates. Melting points were determined in capillary tubes on a Barnstead Electro thermal apparatus and are uncorrected. FT-IR spectra were recorded using KBr disks on an FT-IR SHIMADZU 8400S infrared spectrometer and absorptions were reported as wave numbers (cm^{-1}). NMR spectra were obtained on a FTNMR Bruker Ultra ShieldTM (500-MHz) instrument using CDCl_3 as solvent and TMS as an internal standard. Mass spectra were obtained on a Finnigan Mat 8430 apparatus at ionization potential of 70 eV. Ionic liquids were prepared using available methods. All other reagents were purchased from commercial sources and were freshly used after being purified by standard procedures. All known compounds were identified by comparison of their melting points with authentic samples or reported in the literature and Yields refer to isolated yields.

4.2. Preparation of 1-butyl-3-methylimidazolium chloride [BMIm]Cl

The ionic liquids were prepared and purified by using the procedures described in the literature.⁴⁰ Briefly, [BMIm]Cl was synthesized by direct alkylation of *N*-methylimidazole with an excess amount of 1-chlorobutane in a round-bottom flask along with continuous stirring at $T = 80^\circ\text{C}$ for 48 h under a nitrogen atmosphere. The volatile material was removed from the resulting yellow solution under reduced pressure and remaining light-yellow oil was redissolved in dry acetonitrile and added drop wise to a well-stirred solution of dry ethyl acetate. The imidazolium salt began to crystallize exothermically almost immediately. Then the mixture was cooled at -30°C for 2 hr and the

supernatant solution is removed via filtration and the resulting white solid was dried under reduced pressure. This synthesized ionic liquid was analyzed by ^1H NMR to confirm the absence of any major impurities, and it was found to be in good agreement with that reported in the literature.

4.3. General procedure

In a Pyrex test tube, water (0.5 ml) was added to [BMIm]Cl (0.084 g, 0.5 mmol) and stirred until a viscous liquid was afforded. Afterward, Ketone (1mmol), aromatic aldehyde (2mmol) and NaOH (0.03 g, 0.75 mmol) were added to this solution. The mixture was stirred at room temperature for an appropriate time (Table 5), after completion of the reaction (monitored by TLC), the solid residue was filtered off, washed with water (3×5 mL), dried at 100 °C for 24 hours and recrystallized from ethyl acetate or ethanol to afford pure corresponding α,α' -bis(substituted benzylidene) cycloalkanones.

4.4. Physical and Spectral Data

Compound 5f. Yellow solid (86%). Mp. 282-280 °C; ^1H NMR (500 MHz, CDCl_3): δ 3.17(s, 4H), 3.95 (s, 6H), 7.67(s, 2H), 9/7 (d, $J = 8.4$ Hz, 4H), 1/8(d, $J = 8.35$ Hz, 4H). ^{13}C NMR (125 MHz, CDCl_3) = 26.57, 52.26, 130.20, 130.45, 130.54, 132.91, 139.05, 139.07, 49.166, 27.196; MS (70 eV): m/z (%) = 375(M^+), 361, 345, 317, 258, 129, 115.

Compound 5n. Yellow solid (63%). Mp. 196–198 °C; IR (KBr): 1716, 1272, 1108 cm^{-1} ; ^1H NMR(500 MHz, CDCl_3): δ 1.8-1.7 (m, 2H), 2.9 (m, 2H), 3.9 (s, 6H), 7.5 (d, $J = 8.2$ Hz, 4H), 7.8 (s, 2H), 8.0 (d, $J = 8,3$ Hz, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 22.72, 28.39, 52.17, 126.55, 126.85, 130.07, 135.91, 137.64, 140.26, 166.56, 189.77; MS (70 eV): m/z (%) = 389(M^+), 375, 359, 331, 272, 115.

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