

Synthesis of α,α' -bis-(substitutedbenzylidene)cycloalkanones catalused by using room temperature ionic liquid.

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Abstract— A facile, efficient and green protocol is described for synthesis of α,α' -bis-(substitutedbenzylidene)- cycloalkanones with good to excellent yields by the reaction of cycloalkanones with aromatic aldehydes by using room temperature ionic liquid catalyst at reflux conditions. The catalyst can be recovered and reused at least for four times without apparently loss of activity.

Index Terms— α,α' -bis-(substitutedbenzylidene)-cycloalkanones,room temperature ionic liquid.

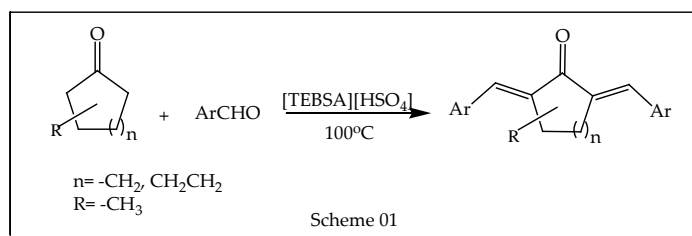
1 INTRODUCTION

Condensation reactions are molecular transformations that join together two molecules to produce a larger molecule and also a smaller molecule (usually water, hence the name condensation). Aldol reactions join two carbonyl containing molecules together forming a new carbon-carbon bond between the alpha carbon of one molecule and the carbon of the carbonyl of the second molecule. This forms a beta hydroxyl carbonyl compound. If this product undergoes a subsequent dehydration, then an aldol condensation reaction takes place.

Cross aldol reaction is an excellent tool for the formation of C-C bond in many classes of carbonyl compounds [1]. Due to the importance of methylene structured unit which is found in many naturally occurring compounds and antibiotics, condensation of cycloalkanones with aromatic aldehydes and ketones is of special interest and crossed aldol condensation is an effective pathway for these preparations [2]. Although studies on the Crossed-aldol reaction have been focused on α -alkylidene- and α,α' -arylidene-carbonyl compounds, interest in α,α' -bisalkylidene and α,α' -bisarylidene-carbonyl compounds is increasing. Particularly, α,α' -bis-(substitutedbenzylidene)- cycloalkanones have been attracting much more attention, not only due to their intriguing biological activities such as antiangiogenic [3,4], quinine reductase inducer [5], arginine methyltransferase inhibitor [6], cytotoxicity [7,8], cholesterol-lowering activity [9], uses in agrochemicals, pharmaceuticals and perfumes [10], in bis-spiropyrrolidines [10–12], and as liquid crystalline polymer

units [13], but also as important precursors for the synthesis of pyrimidine derivatives [14], 2,7-disubstituted tropones [15], and they are the synthetic intermediates of choice to functionalize the α , β -position during the total synthesis of natural products such as the cystodytins [16]. The drug resistance reversal properties of also been reported [17,18]. Moreover, it can be used to synthesize some multifunctional group compounds with special structures via Diels–Alder reaction, Michael addition [19]. Therefore, it is important to develop its new environmentally benign, green and economic synthetic process. The above facts prompted us to synthesize benzylidene cycloalkanone analogs in an efficient and cost effective manner.

Today there is an increasing interest in the use of environmentally feasible reaction conditions using green catalyst and solvent like ionic liquids for such organic synthesis which leads to a clean, efficient, and economical technology. In continuation of our interest to develop greener alternatives for the synthesis of α,α' -bis-(substitutedbenzylidene)- cycloalkanones was developed by using ionic liquid (**Scheme 01**).



2 EXPERIMENTAL PROCEDURE FOR PAPER SUBMISSION

2.1 Material and Methods:

Melting points were measured in open glass capillaries on a Veego melting-point apparatus and were uncorrected. ^1H NMR was recorded at room temperature on a Bruker Avance II 400MHz Spectrometer (SAIF, Punjab University, Chandigarh) in CDCl_3 using TMS as internal standard. IR spectra (using KBr pellets) were obtained with a Perkin Elmer Spectrum RX FTIR (SAIF, Punjab University, Chandigarh) instru-

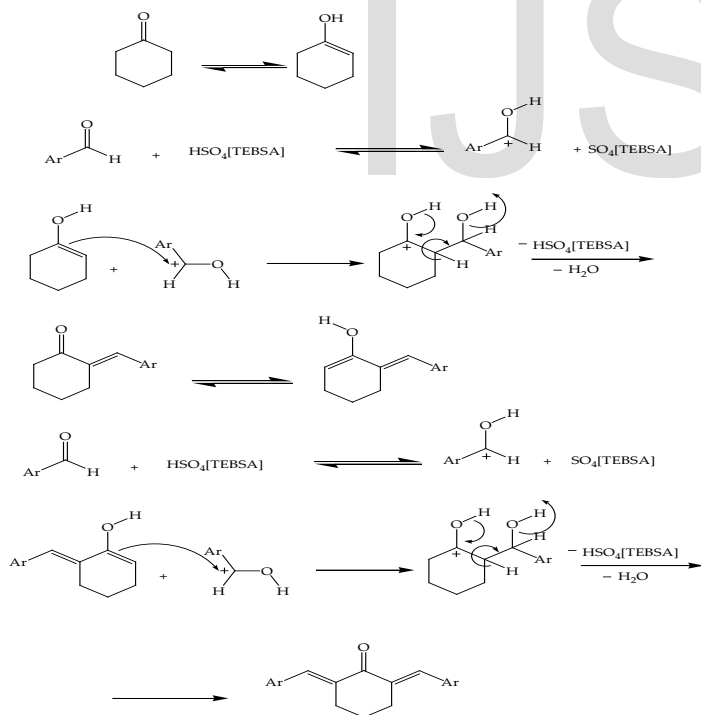
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ment. The reactions were monitored on TLC using pre-coated plates (silica gel on aluminum, Merck). All reagents were obtained from commercial sources and used without further purification. Solvents for chromatography were distilled before use. The products were also characterized by comparison of their melting point with literature values.

2.2 General procedure for synthesis of α,α' -bis-(substitutedbenzylidene)cycloalkanones derivatives at reflux condition:

A mixture of cyclohexanone (5 mmol), aldehyde (10 mmol) and N-(4-sulfonic acid) butyl triethyl ammonium hydrogen sulphate ionic liquid (2.0 mol%) was added to a round bottom flask equipped with reflux condenser. The mixture was stirred at 100°C for a certain period of time to complete the reaction. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled at room temperature. To this reaction mixture water (5 ml) was added and mixture was stirred for 10 minutes in order to dissolve the catalyst. Then the water was evaporated and the catalyst was dried at 65°C under reduced pressure for 2hr and reuse for synthesis. The obtained solid was collected by filtration and recrystallize with ethanol to afford the pure product.

2.3 Mechanism for synthesis of α,α' -bis-(benzylidene)cyclohexanone derivatives:



2.4 Spectral data for some synthesized α,α' -bis-(substitutedbenzylidene)cycloalkanones derivatives at reflux condition:

1] 2,6-bis-(4-nitrobenzylidene) cyclohexanone (Table 03, entry 06): IR (KBr in cm^{-1}) 2921, 1669, 1589, 1512. ^1H NMR (300

MHz, CDCl_3) δ 7.82 (s, 2H), 7.63-7.61 (m, 4H), 7.28 (m, 4H), 2.95-2.98 (t, 4H), 1.85 (m, 2H). ^{13}C NMR (300 MHz, CDCl_3) δ 187.33, 147.79, 145.09, 141.19, 136.59, 127.51, 121.71, 55.35, 27.74, 27.61. MS (EI): m/z 365.

2] 2,6-bis-(4-methoxybenzylidene)-4-methylcyclohexanone (Table 03, entry 12): IR (KBr in cm^{-1}) 2936, 1657, 1594, 1248. ^1H NMR (300 MHz, CDCl_3) δ 7.39-7.37 (d, 4H), 7.69 (s, 2H), 6.87-6.85 (d, 4H), 3.80-3.71 (s, 6H), 3.36 (dd, 2H), 2.85-2.83 (m, 2H), 1.74-1.71 (m, 1H), 1.17 (d, 3H). ^{13}C NMR (300 MHz, CDCl_3) δ 190.33, 159.32, 146.09, 128.74, 128.51, 114.41, 55.35, 37.74, 37.51, 23.05. MS (EI): m/z 335.2.

3 RESULTS AND DISCUSSIONS

In continuation of our interest in green, environmentally benign and efficient procedures, the synthesis of α,α' -bis-(substitutedbenzylidene)-cycloalkanones was developed by using [TEBSA][HSO_4] ionic liquid as a greener alternative. Firstly, reaction of benzaldehyde and cyclohexanone was chosen as the model reaction to optimize the use of [TEBSA][HSO_4] ionic liquid for synthesis of corresponding 2,6-dibenzylidene cyclohexanone. The results are summarized in (Table 01). Ionic liquid shows the best catalytic effect at 2.0 mol% producing 93% of yield for 30 minutes. The generality of the reaction also checked at room temperature for 2.0 mol% (Table 01, entry 7). The results were satisfactory and even if the amount of catalyst increased the corresponding 2,6-dibenzylidene cyclohexanone gives the same yield (Table 01).

Table 01: Optimization of catalyst for reaction of benzaldehyde and cyclohexanone at 100°C.

Entry	Amount of catalyst used (%)	Reaction conditions	Yield in %
1	0 mol	Reflux/ 2hr	0
2	0.5 mol	Reflux/1hr	Trace
3	1.0 mol	Reflux/1hr	60
4	1.5 mol	Reflux/1hr	78
5	2.0 mol	Reflux/30min.	93
6	2.5 mol	Reflux/30 min.	93
7	2.0 mol	RT/3hr	76

To establish the generality and scope of the ionic liquid as a catalyst for this synthesis, various aldehydes and cyclohexanone/cyclopentanones were reacted following optimized method to prepare a series of α,α' -bis-(substitutedbenzylidene)-cycloalkanones. Several examples illustrating this novel and general method for the synthesis of α,α' -bis-(substitutedbenzylidene)-cycloalkanones are summarised in (Table 03). In all these cases, the corresponding products were obtained in high to excellent yields at low reaction time. Aromatic aldehydes containing both electron donating and electron withdrawing groups underwent the conversion smoothly and gave the products in good to excellent yields (Table 03). The aldehydes containing electron withdrawing groups gave

cleaner reactions with higher yields at short reaction time than the aldehydes which contain electron donating groups. It is observed that electron withdrawing groups in aromatic ring increases the reactivity of aldehydes.

Table 02: Reuse of catalyst for the condensation reaction between benzaldehyde and cyclohexanone.

Reuse of catalyst	Time in min.	Temp. (°C)	Yield (%)
Fresh	30	100	93
I reuse	30	100	91
II reuse	30	100	91
III reuse	30	100	89
IV reuse	30	100	87
V reuse	30	100	81

The reuse of the catalyst is a major factor in a new synthetic green procedure. The ionic liquid can be reused after simple distillation to remove water and remaining ionic liquids was dried under vacuum and reuse for further reactions. To test this, a series of five consecutive runs of the reaction of benzaldehyde and cyclohexanone with catalyst were carried out. The results, however, demonstrated no significant change in the activity of the catalyst. The results in (Table 02) show loss of activity over five recycles. This method offers some advantages in terms of low reaction times, simplicity of performance, low cost and use of ionic liquid as a green catalyst and solvent which follow along the line of green chemistry.

Table 03: Synthesis of α,α' -bis-(substitutedbenzylidene)- cycloalkanones derivatives by using ionic liquid.

Entry	Aldehyde	Cycloketones	Time (Min)	Yields(%) ^a	M.P. (°C)
1	C ₆ H ₅	Cyclohexanone	30	93	118
2	4-Cl- C ₆ H ₄	Cyclohexanone	20	97	148
3	3-NO ₂ -C ₆ H ₄	Cyclohexanone	10	92	190
4	4-OCH ₃ -	Cyclohexanone	15	90	162
5	C ₆ H ₄	Cyclohexanone	25	88	168
6	4-CH ₃ - C ₆ H ₄	Cyclohexanone	10	98	172
7	4-NO ₂ - C ₆ H ₄	Cyclohexanone	25	82	90
8	3-F- C ₆ H ₄	Cyclohexanone	15	90	166
9	2,4-Cl- C ₆ H ₃	4-Methyl- Cyclohexanone	35	90	102
10	C ₆ H ₅	4-Methyl- Cyclohexanone	10	94	160
11	4-Cl-C ₆ H ₄	4-Methyl- Cyclohexanone	25	91	176
12	3-NO ₂ -C ₆ H ₄	4-Methyl- Cyclohexanone	10	93	140
13	4-OCH ₃ -	4-Methyl- Cyclohexanone	15	90	128
14	C ₆ H ₄	Cyclopentanone	15	92	190
15	4-CH ₃ - C ₆ H ₄	Cyclopentanone	10	94	216
16	C ₆ H ₅	Cyclopentanone	12	95	244
17	4-OCH ₃ -	Cyclopentanone	10	97	236
	C ₆ H ₄				
	4-CH ₃ - C ₆ H ₄				
	4-Cl- C ₆ H ₄				

^aAll yields refer to isolated yields. All the products were characterized by IR spectra, mass spectra, ¹H NMR, ¹³-C NMR spectroscopy.

4 CONCLUSION

In conclusion we have developed a simple, efficient and green protocol for the cross aldol condensation reaction of different aldehydes with cyclic ketones at 100°C temperature to give the corresponding substituted benzylidene cycloalkanones with good to excellent yields. The mild reaction conditions, shorter reaction time, easy work up procedure, good to excellent yields, avoiding the use of hazardous organic solvent and reuse of catalyst are the major advantages of the present protocol. In addition of this Ionic liquid was successfully reused for four runs without potential loss of activity is the great advantage of this method. Thus results shows that this is a po-

tential green alternative to traditional method for synthesis of substituted benzylidene cycloalkanones.

5. ACKNOWLEDGMENT

Author thanks to University Grant Commission, New Delhi for providing Rajiv Gandhi Senior Research Fellowship for financial support.

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