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A simple, improved and solvent free synthesis of α, α'-bis(arylidene)cycloalkanones

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ABSTRACT

A green and efficient procedure for the synthesis of α, α'-bis(arylidene) cycloalkanones has been developed by grinding aryl aldehydes with cycloalkanones in the presence of activated barium hydroxide (C-200), in a pestle mortar with out any solvent. This is an environmentally benign protocol which not only excludes the use of organic solvents and radiations for the reaction but also gives product in good yield (84-93%) with in few minutes (3-5 min.).

Key words: Aryl aldehydes, cycloalkanones, grinding, activated barium hydroxide, solvent and radiation free.

INTRODUCTION

α, α'-Bis(arylidene)cycloalkanones constitute an important class of α-β unsaturated carbonyl compounds as they play an important role in organic synthesis [1] and are the starting materials for the synthesis of different saturated and partially saturated heterocyclic ring systems [2]. These are important precursors for the synthesis of bioactive pyrimidine derivatives [3] and synthetic intermediates to functionalize α-β position during the total synthesis of natural products such as cystodytins [4]. Some of them exhibit anticancer properties [5] and are also used as ligands for the synthesis of complexes of industrial applications [6].

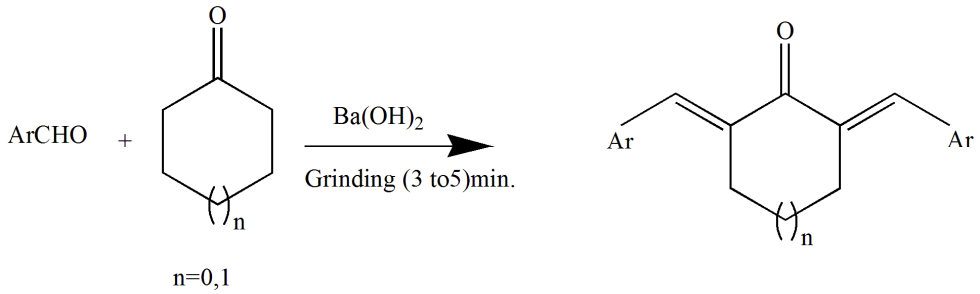
Cross aldol condensation, which is a powerful tool for the formation of C-C bond, is also an important protocol for the synthesis of α,α'-bis(arylidene)cycloalkanones. Cross aldol condensation of cycloalkanones with aromatic aldehydes leading to the formation of the title compounds has been catalysed by strong acids [7] more likely by strong bases [8], using either traditional heating [8] or microwave heating [9]. However in most of the cases reaction suffers reverse and / or side reactions [10]. So a variety of new reagents have been introduced as catalyst for this reaction such as $InCl_3$[11], $InCl_3$ /ionic liquid [12], $BF_3.OEt_2$ [13], $FeCl_3$ [14], SmI_3 [15], TMSCl/NaI [16], $Yb(OTF)_3$ [17], KF with inorganic solid support [18], metal complexes [19], KF-Al_2O_3/MW [20], $LiClO_4/Et_3N$ [21], SiO_2-OK/C_2H_5OH [22], BMPTO/MW [23], $RuCl_3$ [24], I_2 [25], AcONa/ AcOH [26] , NKC-9 [27]. But still many of these methods suffer one or more drawback of hazardous conditions, poor yields, longer reaction times, high temperature, low chemo selectivity and expensive reagents (table-1). Also in some cases formation of side products make the purification more difficult.

Table 1: Comparison of the results of the reactions carried out with different catalyst for the synthesis of α, α'-bis (arylidene) cycloalkanones and the present one.

Entry	Catalysts	Time	Temp.^{0}C	Yield (%)	Ref.
1	$InCl_3.4H_2O$	6-12 Hrs.	110(Sealed tube)	89-95	11
2	$InCl_3$/ionicliquid	5-6 Hrs	100	78-82	12
3	SmI_3/ ionic liquid	3-4.5 Hrs.	Room temp.-60	80-98	15a
4	SmI_3/THF	4-6 Hrs.	Room temp.-80	71-85	15b
5	TMSCl/NaI	60-80 Min.	Room temp.	72-95	16
6	$Yb(OTF)_3$	4-12 Hrs.	90	88-97	17
7	KF/Al_2O_3	5 Min.	M.W	73-82	20b
8	$NaOH/C_2H_5OH$	2 Min.	M.W.	90-95	9
9	$LiClO_4/Et_3N$	1Min-4days	Room Temp.	74-100	21
10	SiO_2-OK/C_2H_5OH	1.5-4.5 Hrs.	Reflux	84-98	22
11	BMPTO	5-10 Min.	M.W	53.5-93.4	23
12	$RuCl_3$	4-24 Hrs.	120(Sealed tube)	82-95	24
13	I_2 / CH_2Cl_2	4.5-9.5 hrs.	room temp.	89-95	25
14	AcONa, AcOH	3-8 hrs.	120	78-83	26
15	NKC-9	4-6 hrs.	reflux	75-94	27
16	$Ba(OH)_2$/Grinding*	3-5 Min.	Room Temp.	84-93	*

* *Present Method.*

As now a days, more emphasis is being laid on development of reactions under eco-friendly conditions by eliminating the use of hazardous chemicals particularly solvents because of their volatile nature. Therefore attempts have been made by the chemists to carry out the reactions in solid phase or solvent free conditions using microwave radiations [28] or grinding technique [29]. Working on the lines of development of simpler and milder routes for the transformations in organic synthesis [30], we tried to develop a new and milder approach for the synthesis of α, α'-bis (arylidene)cycloalkanones, which involves the use of catalyst of high activity, easy availability, short reaction time and simple work up procedure.



n=0,1

Fig. I Synthesis of α, α'-bis (arylidene)cycloalkanones

MATERIALS AND METHODS

Experimental

The reaction by grinding was carried out in a china pestle mortar at room temperature. During the grinding, change in colour took place which indicates the progress of reaction. Conversion of entire reaction mixture to a yellow solid mass indicates the completion of reaction. All the products obtained were characterized from their ^{1}H NMR, IR spectra and melting points comparison with the literature values. The ^{1}H NMR spectra were recorded on Bruker Avance II 400 spectrometer at 400 MHz in $CDCl_3$ using TMS as internal standard. The IR spectra were recorded using Perkin Elmer spectrometer (KBr plates).

General procedure for the synthesis of α, α'-bis(arylidene)cycloalkanones (1-12):

A mixture of aryl aldehyde (4.8 mmole), cycloalkanone (2.35 mmole) and activated barium hydroxide (1.5gm, 8.7 mmole) was ground at room temperature for 3 to 5 minutes, when it gets converted to a yellow solid mass. The reaction mixture was allowed to stand for 10 minutes at room temperature. 20 ml of ice cold water was added to the

reaction mixture and acidified with conc. HCl, when solid product separated out. The product so obtained was collected by suction filtration and recrystallized from ethanol.

Table II: Synthesis of α, α'-bis(arylidene)cycloalkanones

Entry	Ar.	n	Grinding time[b] (min.)	Yields (%)[a]	M.P. (°C) Found (Lit.)	Ref
1	C_6H_5	0	3	91	189-190 (188-189)	23
2	*p*-$NO_2C_6H_4$	0	5	84	228-230 (230-231)	23
3	*p*-MeO C_6H_4	0	3	93	210-211 (212)	24
4	*p*-ClC_6H_4	0	5	85	225-226 (224-225)	15b
5	*p*- CH_3 C_6H_4	0	4	91	184-185 (183-184)	15b
6	C_6H_5 CH=CH	0	4	88	223-224 (222-224)	23
7	C_6H_5	1	3	90	117-118 (117-118)	17
8	*p*-NO_2 C_6H_4	1	5	87	158-159 (160)	23
9	*p*-MeO C_6H_4	1	3	92	202-203 (203-204)	17
10	*p*-ClC_6H_4	1	5	88	146-147(147-148)	27
11	*p*- CH_3 C_6H_4	1	4	93	169-170 (172-173)	15b
12	C_6H_5 CH=CH	1	4	89	179-180 (180)	23

[a] *Isolated yield,* [b] *Grinding was done till a yellow solid mass was formed.*

Spectral data of the compounds synthesized are given below.

2,6-Bis(benzylidene)cyclohexanone(1)
IR (KBr): 1664 cm^{-1}(C=O); ^{1}H-NMR ($CDCl_3$): δ 1.72-1.88 (m, 2H, 4-CH_2), 2.82 -2.98 (m, 4H, 3 & 5 -CH_2) 7.23-7.55 (m, 10H, Ar-H), 7.80 (s, 2H, 2 × = CH).

2,6-Bis(4-nitrobenzylidene)cyclohexanone(2)
IR (KBr): 1669 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 1.85- 1.87 (m, 2H, 4-CH_2), 2.94 (t, J = 6.0 Hz, 4H, 3 & 5 -CH_2), 7.56-8.20 (m, 8H, Ar-H), 8.30 (s, 2H, 2 × = CH).

2,6-Bis(4-methoxybenzylidene)cyclohexanone(3)
IR (KBr): 1661cm^{-1}(C=O); ^{1}H-NMR ($CDCl_3$): δ 1.72-1.84 (m, 2H, 4-CH_2), 2.91 (t, J= 5.4 Hz, 4H, 3 & 5-CH_2), 3.78 (s, 6H, 2 × OCH_3), 6.96-7.48 (m, 8H, Ar-H), 7.75(s, 2H, 2 × = CH)

2,6-Bis(4-chlorobenzylidene)cyclohexanone(4)
IR (KBr): 1667 cm^{-1}(C=O); ^{1}H-NMR ($CDCl_3$): δ 1.81 -1.85 (m, 2H, 4-CH_2), 2.86-2.93 (t, J=6.0 Hz, 4H, 3 & 5 -CH_2), 7.36-7.39 (m, 8H, Ar-H), 7.73 (s, 2H, 2 × = CH)

2,6-Bis(4-methylbenzylidene)cyclohexanone(5)
IR (KBr): 1661 cm^{-1}(C=O); ^{1}H-NMR ($CDCl_3$): δ 1.72-1.77 (m, 2H, 4-CH_2), 2.35 (s, 6H, 2 × CH_3), 2.92 (t, J= 5.6 Hz, 4H, 3 & 5 -CH_2), 7.18-7.43 (m, 8H, Ar-H), 7.76 (s, 2H, 2 × = CH).

2,6-Bis(cinnamylidene)cyclohexanone(6)
IR (KBr): 1690 cm^{-1}(C=O); ^{1}H-NMR ($CDCl_3$): δ 1.75 (m, 2H, 4-CH_2), 2.72-275 (t, J = 5.6 Hz, 4H, 3 & 5 -CH_2), 6.96-7.44 (m, 16H, Ar-H, 6 × = CH).

2,5-Bis(benzylidene)cyclopentanone(7)
IR (KBr): 1675 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ 3.10 (s, 4H, 3 & 4-CH_2), 7.35-7.45 (m, 10H, Ar-H), 7.58 (s, 2H, 2 × = CH).
2,5-Bis(4-nitrobenzylidene)cyclopentanone(8)
IR (KBr): 1686 cm^{-1}(C=O); ^{1}H-NMR ($CDCl_3$): δ 3.20 (s, 4H, 3 & 4 -CH_2), 7.65-8.30 (m, 10H, Ar-H, 2 × = CH).

2,5-Bis(4-methoxybenzylidene)cyclopentanone(9)
IR (KBr): 1692 cm^{-1}(C=O); ^{1}H-NMR ($CDCl_3$): δ 3.08 (s, 4H, 3 & 4-CH_2), 3.80 (s, 6H, 2 × OCH_3), 6.92 – 7.57 (m, 10H, 8 Ar-H & 2 × = CH).

2,5-Bis(4-chlorobenzylidene)cyclopentanone(10)
IR (KBr): 1620 cm^{-1}(C=O); ^{1}H-NMR ($CDCl_3$): δ 3.11 (s, 4H, 3 & 4 -CH_2), 7.29-7.65 (m, 10H, Ar-H & 2 × = CH)

2,5-Bis(4-methylbenzylidene)cyclopentanone(11)
IR (KBr): 1700 cm^{-1}(C=O); ^{1}H-NMR ($CDCl_3$): δ 2.35 (s, 6H, 2 × CH_3), 3.06 (s, 4H, 3 & 4 -CH_2), 7.12-7.57 (m, 10H, Ar-H, & 2 × = CH).

2,5-Bis(cinnamylidene)cyclopentanone(12)
IR (KBr): 1670 cm^{-1}(C=O); ^{1}H-NMR ($CDCl_3$): δ 2.93 (s, 4H, 3 & 4 -CH_2), 6.98-7.53 (m, 16H, Ar-H, 6 × = CH).

RESULTS AND DISCUSSION

The present method is a very mild, economical and environmentally benign procedure for the synthesis of α, α'-bis(arylidene)cycloalkanones, which involves the grinding of aryl aldehydes with cycloalkanones in the presence of activated barium hydroxide in a pestle with mortar without any solvent for 3 to 5 minutes (Fig. 1). Transition in colour of the reaction mixture from colourless to yellow, during grinding indicates the completion of reaction as confirmed by TLC. Though reaction completes during grinding period, yet it was left at room temperature so that at every point of the reaction mixture completion of the reaction may take place. The product formed was easily obtained by just acidifying the reaction mixture without extraction in highly improved yield.

We also tried the other bases for this condensation reaction, but the results obtained proved, activated barium hydroxide as a superior solid base catalyst compared to other bases. When activated barium hydroxide was replaced with strong alkali bases such as NaOH or KOH reaction mixture turned dark and product could not be isolated. With Hydrated barium hydroxide and weak bases such as $Ca(OH)_2$ and $Mg(OH)_2$ reaction could not be completed even after keeping the reaction mixture for many hours after grinding. To find out the optimum amount of activated barium hydroxide required for efficient conversion, the reaction of cyclohexanone with benzaldehyde was repeated with different equivalent amount of activated barium hydroxide and yields were found to be more and time was less when 3 to 4 molar equivalent of activated barium hydroxide with respect to ketone was used.

We studied the scope of the reaction by condensing variously substituted aryl aldehydes with cyclopentanones and cyclohexanones to obtain α,α'-bis(arylidene)cyclopentanones or α,α'-bis(arylidene)cyclohexanones respectively in high yield. Barium hydroxide is a valuable reagent because of its textural properties and microcrystallines structures [31] and has also been reported for the synthesis of chalcone in solvent [31] as well as solvent free medium [30a,32]. Activated $Ba(OH)_2$ is a mixture of anhydrous $Ba(OH)_2$ and the monohydrate in variable ratios [31]. The common form of activated $Ba(OH)_2$ is referred as C-200. The efficiency of the activated barium hydroxide as catalyst in these condensation reactions appears due to its appropriate crystalline structure [31] and the nature of adsorbed carbanion and aldehyde on it [33].

CONCLUSION

Thus in general on the basis of results obtained it can be concluded that, grinding using activated barium hydroxide is better choice for the synthesis of the title compounds at room temperature than the conventional and reported methods in terms of safety, reaction time , yield, economy and simplicity. This method not only excludes the solvent for reaction but also for extraction process, hence it is environmentally benign procedure for the synthesis of α,α'-bis(arylidene)cycloalkanones at room temperature, involving simple workup procedure.

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