

Highly Efficient Synthesis of α,α' -Bis-(substituted-benzylidene) Cycloalkanones using $\text{HBF}_4\text{-SiO}_2$ under Solvent-Free Conditions

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Abstract:- Highly efficient and clean procedure is described for the synthesis of α,α' -bis-(substituted-benzylidene) cycloalkanones with excellent yields by the reaction of cycloalkanones with aromatic aldehydes using catalytic amount of $\text{HBF}_4\text{-SiO}_2$ as catalyst. The catalyst was easily recovered and reused without loss of activity.

Keywords:- α,α' -bis-(substituted-benzylidene) cycloalkanones, $\text{HBF}_4\text{-SiO}_2$, solvent-free conditions.

I. INTRODUCTION

➤ Important features of the present protocol

- It is the fastest method as compared to literature reported methods.
- The electron donating as well as withdrawing aryl aldehydes were successfully transformed into corresponding α,α' -bis-(substituted-benzylidene) cycloalkanones.
- Simple work up procedure, inexpensive and easily available catalyst makes the protocol economically attractive and nice for industrial large scale production.
- This is a truly catalytic with least loading (2 mol %) of the catalyst under solvent free conditions.
- This methodology is general as variety of aldehydes and ketones furnish corresponding α,α' -bis-(substituted-benzylidene) cycloalkanones in excellent yields.
- Short reaction time, recyclability and reusability of the catalyst are the note worthy and attractive features of the present protocol.

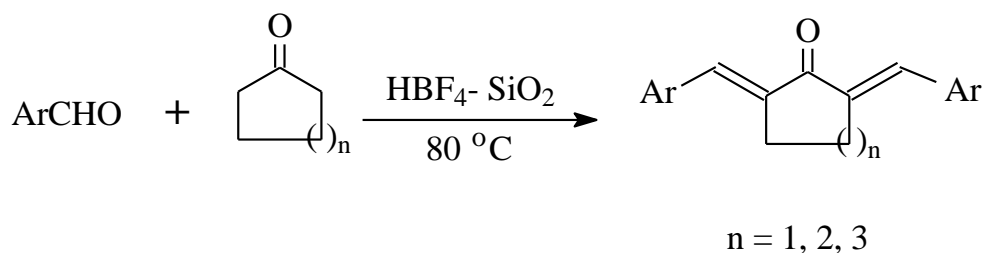
The α,α' -bis-(substituted-benzylidene) cycloalkanones are useful intermediates for the synthesis of bioactive pyrimidines,¹ agrochemicals, pharmaceuticals and perfumes² liquid crystalline polymers,³ and bis-pyrrolidines.^{4,5} Generally, benzylidenecycloalkanones are prepared by cross-aldol condensation of cycloalkanones with aldehydes in the presence of strong acids or bases. However, these protocols often suffer from reverse and side reactions and therefore give low yields of products.⁶ Variety of catalytic procedures⁷ using different complexes of metal (II) ions is reported to give low yields (38%) of

enone products. In other cases, TMSCl/NaI ,⁸ LiOH ,⁹ I_2 ,¹⁰ $\text{KF-Al}_2\text{O}_3$,¹¹ BMPTO ,¹² $\text{Mg}(\text{HSO}_4)_2$,¹³ Cp_2TiPh_2 ,¹⁴ polymer-supported sulphonic acid,¹⁵ $\text{InCl}_3.4\text{H}_2\text{O}$,¹⁶ FeCl_3 ,¹⁷ aqueous micellar media,¹⁸ have also been used. However, in most cases the yields are good at high temperatures and some of the reagents require longer reaction times and complicated purification procedures. Use of $\text{Yb}(\text{OTf})_3$,¹⁹ $\text{Cu}(\text{OTf})_3$,²⁰ RuCl_3 ,²¹ SmI_3 ,²² as catalysts has been reported with good yields. But all these procedures demand reactions to be carried out in sealed tubes at high temperatures. Therefore, there is still scope to develop a more efficient method for the preparation of these compounds.

The toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in organic synthesis have posed serious problems to the environment. Therefore, the possibility of performing chemical processes in the absence of solvent (solvent-free conditions) has been receiving more attention.^{23,24} Recently, because of increased environmental concerns and strong economic driver in chemical research and industry, great efforts have been made on heterogeneous catalysis,²⁵ which allows the catalyst for easy isolation and recycling. Thus, solid-supported catalysts have drawn considerable attention in organic synthesis due to their advantages such as environmental compatibility, reusability, high selectivity, simple operation, non-corrosiveness and low cost. Among of many solid-supported catalysts employed, silica-supported fluoroboric acid ($\text{HBF}_4\text{-SiO}_2$), one of the important environmentally benign silica-supported catalysts,²⁶ has already been developed in organic chemistry.²⁷

II. RESULTS AND DISCUSSION

As part of our program aiming at developing new, selective and environmental friendly methodologies for the preparation of fine chemicals employing $\text{HBF}_4\text{-SiO}_2$ as a catalyst,^{28,29} we wish to describe herein highly effective protocol for the synthesis of α,α' -bis(substituted benzylidene) cycloalkanones from the reaction of aldehydes with cycloalkanones under solvent-free conditions (**Scheme 1**).



Scheme 1. Synthesis of a,a'-Bis-(substituted-benzylidene) cycloalkanones using $\text{HBF}_4\text{-SiO}_2$ under solvent-free conditions

Initially a systematic study was carried out for catalytic evaluation of $\text{HBF}_4\text{-SiO}_2$ for the condensation of benzaldehyde (2 mmol) with cycloalkanones (1 mmol) under various conditions at 80 °C (Table 1). After many studies, we found that when less than 2 mol% of $\text{HBF}_4\text{-SiO}_2$ was applied lower yields of the corresponding product (Table 1, entries 2-5) resulted, whereas use of more than 2 mol% did not improve the yield (Table 1, entries 7-8). When attempts were made to carry out this reaction in the absence of $\text{HBF}_4\text{-SiO}_2$, the substrate was recovered almost quantitatively (Table 1, entry 1).

Table 1. A catalytic study of $\text{HBF}_4\text{-SiO}_2$ during the reaction of benzaldehyde (2mmol) with cyclohexanone (1mmol) at 80 °C under solvent-free conditions

Entry	$\text{HBF}_4\text{-SiO}_2$ (mol%)	Time min/[h]	Yield (%)
1	—	[05]	—
2	0.1	30	60
3	0.3	25	70
4	0.5	15	80
5	1.0	10	85
6	2.0	05	94
7	3.0	05	94
8	4.0	05	94

Next, we studied the effect of various solvents and the results of the reaction of benzaldehyde (2mmol) with cyclohexanone (1mmol) using 2 mol% $\text{HBF}_4\text{-SiO}_2$ at 80 °C in the presence of various solvents are shown in **Table 2**.

When organic solvents such as nitromethane, tetrahydrofuran (THF), acetonitrile, dichloromethane (DCM), and chloroform was used for this reaction, the desired product was obtained in low yields (Table 2, entries 2-6). Whereas, an excellent yield of the desired product was obtained when the reaction was carried out at 80 °C under solvent-free conditions (Table 2, entry 1). These results led to the suggestion that solvent-free conditions are best suited for this reaction.

Table 2. Investigation of various solvents

Entry	Solvent	Time min	Yield (%)
1	neat	5	94
2	MeNO ₂	130	45
3	THF	110	55
4	MeCN	100	57
5	DCM	100	48
6	CHCl ₃	100	42

To evaluate the scope and generality of the catalyst, the reactions of cyclopentanone, cyclohexanone and cycloheptanone with other aryl aldehydes were conducted. The results were summarized in Table 3.

It is important to mention that the substituted groups of aryl aldehydes such as methoxy, methyl, hydroxy, chloro, and nitro groups are well tolerated under the reaction conditions to afford the desired products in high yields (Table 3, entries 2 - 8 and 13 - 18). α , β -unsaturated aldehyde and heterocyclic aldehydes also afforded the desired product in high yields (Table 3, entries 9-11 and 19,20). Under the present conditions, all reactions were clean and free from any by-product, whereas, by-products are normally observed in classical conditions.³⁰

The advantage of the use of heterogeneous catalyst for this transformation is the ease of catalyst/substrate separation. In our process, when the catalytic reaction was completed, HBF₄-SiO₂ could be recovered conveniently from the reaction mixture through filtration and subsequent washing with ethyl acetate. Then, efforts were made to examine the reusability of HBF₄-SiO₂ by using benzaldehyde and cyclohexanone as a model substrate and the results are described in typical experimental procedure.

Table 3. Preparation of α,α' -Bis(substituted benzylidene) cycloalkanones catalyzed by HBF₄-SiO₂ at 80°C for the time given under solvent free conditions^a.

Entry	Ar.	n	Time (min)	Product	Yield(%) ^b
1.	C ₆ H ₅	1	5	3a	93
2.	p-MeOC ₆ H ₄	1	6	3b	94
3.	p-MeC ₆ H ₄	1	6	3c	95
4.	p-Me ₂ NC ₆ H ₄	1	6	3d	93
5.	p-HOC ₆ H ₄	1	7	3e	91
6.	p-ClC ₆ H ₄	1	5	3f	95
7.	2,4-Cl ₂ C ₆ H ₃	1	5	3g	96
8.	p-NO ₂ C ₆ H ₄	1	11	3h	91
9.	C ₆ H ₅ CH=CH	1	6	3i	95
10.	2-furyl	1	7	3j	91
11.	3-pyridyl	1	6	3k	87
12.	C ₆ H ₅	2	5	3l	94
13.	p-MeOC ₆ H ₄	2	6	3m	90
14.	p-MeC ₆ H ₄	2	6	3n	93
15.	p-Me ₂ NC ₆ H ₄	2	10	3o	94
16.	p-HOC ₆ H ₄	2	5	3p	93
17.	2,4-Cl ₂ C ₆ H ₃	2	5	3q	93
18.	p-NO ₂ C ₆ H ₄	2	11	3r	93
19.	C ₆ H ₅ CH=CH	2	5	3s	95
20.	2-thienyl	2	8	3t	90
21.	C ₆ H ₅	3	6	3u	92

^aRefluxed at 80°C for the time given under solvent-free conditions.

^b Isolated yield.

III. EXPERIMENTAL

A. General

All chemicals were purchased from Sigma-Aldrich and Merck Chemical Companies. All reactions were monitored by thin layer chromatography (TLC) using aluminum plates coated with silica gel (Merck) using 10% ethyl acetate and 90% hexane as eluent. The silica gel (230-400 mesh) for column chromatography was purchased from Spectrochem Pvt. Ltd., India. The products were characterized by comparison of their spectral and physical data with those of authentic samples. All authentic α,α' -bis-(substituted-benzylidene) cycloalkanones were prepared from the corresponding cyclohexanone and benzaldehyde according to the method described in Vogel.³¹ IR spectra were recorded on Nicolet (impact 400D model) FTIR Spectrometer. ¹H NMR spectra were recorded on a Bruker DRX-300 AVANCE at 300 MHz instrument using TMS as internal standard and DMSO-*d*₆ or CDCl₃ as solvent. Mass spectra was obtained by using a GC-MS Hewlett Packard (EI, 20 eV) instrument. All yields refer to isolated ones.

B. Preparation of HBF₄-SiO₂²⁷

HBF₄ (1.65 g, as a 40% aqueous solution) was added to the suspension of silica gel (13.35 g, 230–400 mesh) in diethyl ether (40 mL). The mixture was concentrated and the residue dried under vacuum at 100 °C for 72 h to afford HBF₄-SiO₂ (0.5 mmol g⁻¹) as a free flowing powder.

C. Typical experimental procedure

A mixture of cyclohexanone (5 mmol) and benzaldehyde (10 mmol) was stirred at 80 °C in the presence of a catalytic amount of HBF₄-SiO₂ (200 mg, 0.10 mmol) for an appropriate time (Table 3). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with ethyl acetate (10 mL) and the catalyst was allowed to settle down. The supernatant ethyl acetate was decanted off, washed with ethyl acetate (5 mL) and the combined ethyl acetate layer concentrated under reduced pressure to afford crude product, which was purified by recrystallization from ethanol to afford pure 2,6-dibenzylidenecyclohexanone (94%). The recovered catalyst, without activation, was reused for four more consecutive reactions of cyclohexanone (5 mmol) and benzaldehyde (10 mmol) affording 91, 89, 86, 84% yields, respectively, in 10, 15, 20, and 25 min.

D. Supporting information:

2, 6-dibenzylidenecyclohexanone (31).

Mp 116 – 117 °C (Lit²⁰ Mp 117 – 118 °C); IR (KBr): 771, 1168, 1274, 1435, 1606, 1660, 3020, 3075 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 1.70 – 1.77 (m, 2H), 2.95 (t, *J* = 5.8 Hz 4H), 7.28 – 7.42 (m, 10H), 7.75 (s, 2H); ES-MS *E/Z* 274(M⁺).

IV. CONCLUSION

In summary, we have developed a simple and efficient methodology for the synthesis of α,α' -bis-(substituted-benzylidene) cycloalkanones via condensation reaction of aryl aldehydes and cycloalkanones in the presence of catalytic amount of HBF₄-SiO₂ under solvent-free conditions. The significant features of the method such as requirement of low amount of catalyst, non-aqueous work-up, high yields, and ease of product isolation makes this method an attractive contribution to existing methodologies.

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