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RESEARCH LETTER

A facile synthesis of α,α' -bis(substituted benzylidene) cycloalkanones catalyzed by *p*-TSA under solvent-free conditions

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Various 2,6-dibenzylidene cycloalkanones were readily prepared in a few minutes with good yields by simply mixing aromatic aldehydes with cycloalkanones in the presence of catalytic amounts of *p*-toluenesulfonic acid as a solid heterogeneous catalyst under solvent-free condition.

Keywords: α,α' -bis(substituted benzylidene) cycloalkanones; *p*-toluenesulfonic acid; cross-aldol condensation; aldehydes; green chemistry

Introduction

Cross-Aldol condensation of aromatic aldehydes with cycloketones is an important synthetic reaction for the preparation of α,α' -bis(substituted benzylidene) cycloalkanones. These benzylidene derivatives are intermediates of various pharmaceuticals, agrochemicals, and perfumes (1). They are frequently used for the synthesis of biological activities such as HIV-1 integrase inhibitory (2), bioactive pyrimidine compounds (3). They also find applications in the preparation of nonlinear optical materials (4) and liquid-crystalline polymers (5).

The typical methods for the preparation of α,α' -bis(substituted benzylidene) cycloalkanones generally involve the cross-aldol condensation of cycloalkanone with aldehydes under strong acids or bases (6). However, this process suffers from reverse and side reactions resulting in low yields of the products.

Different complexes of metal(II) ions have also been used as catalysts but the yields were not satisfactory (7). Various other reagents such as BMPTO (8), KF–Al₂O₃ (9), FeCl₃ (10), Yb(OTf)₃ (11), Cu(OTf)₂ (12), I₂ (13), and animal bones meal (14) are known to catalyze the reaction. However, in most cases the yields are good at high temperatures and some of the reagents require longer reaction times and tedious purification procedures. Thus, there is a certain need for the development of an alternative route for the production of α,α' -bis(substituted benzylidene) cycloalkanones, which surpasses those limitations.

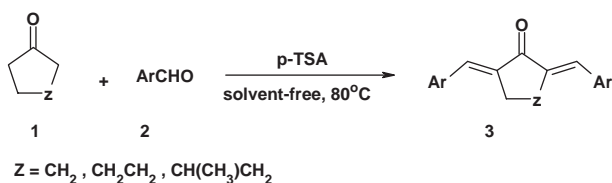
During the course of our systematic studies directed toward the development of environmentally friendly procedures for several important organic transformations (15–18) herein we describe an efficient method for the synthesis of α,α' -bis(substituted benzylidene) cycloalkanones through reaction of aldehydes with cycloalkanones in the presence of catalytic amounts of *p*-toluenesulfonic acid under solvent-free condition (Scheme 1).

In the organic synthesis and reactions, increasing attention is being focused on green chemistry using environmentally benign reagents and conditions, particularly solvent-free procedures, which often lead to clean, eco-friendly and highly efficient procedures involving simplified work-ups. The use of solid acid catalysts has gained a vast importance in organic synthesis due to their several advantages such as operational simplicity, no toxicity, reusability, low cost, and easy isolation after completion of reaction. In recent years *p*-toluenesulfonic acid (*p*-TSA) has been considered as an efficient, inexpensive, and readily available catalyst for several organic transformations (19–21). Because of the application of this catalyst for development of useful synthetic methodologies we have observed that this is very suitable to catalyze the cross-Aldol condensation of aromatic aldehydes with cyclic ketones at 80°C under solvent-free conditions.

Results and discussion

Firstly, reaction of benzaldehyde and cyclohexanone was chosen as the model reaction to detect whether

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Scheme 1. Synthesis of α, α' -bis(substituted benzylidene) cycloalkanones

the use of *p*-TSA was efficient and to investigate the optimized conditions. The best result was achieved by carrying out the reaction in the presence of 20 mol% of *p*-TSA with 2:1 mole ratios of benzaldehyde and cyclohexanone at 80°C for 20 min (Table 1, Entry 1). To establish the generality and scope of *p*-TSA as a catalyst for this synthesis, various aldehydes (2) and cycloalkanones (1), was reacted following the optimized method to prepare a series of α, α' -bis(substituted benzylidene) cycloalkanones. Several examples illustrating this novel and general method for the synthesis of **3a-t** are summarized in Table 1. In all these cases, the corresponding products were obtained in low reaction times with good yields.

Aromatic aldehydes containing both electron donating and withdrawing groups underwent the conversion smoothly and gave the products in good to excellent yields (Table 1). So it is concluded that the electronic nature of the substituents has no significant effect on this reaction. However, the reaction of *p*-chlorobenzaldehyde with cyclohexanone (Entry 2) gives a relatively high yield, when compared with other aromatic aldehydes.

All the reactions were free from by-products, which are generally found in classical reactions conditions. The structure of the products was deduced from their IR, ¹H NMR, and ¹³C NMR.

To illustrate the need of *p*-TSA for these reactions an experiment was conducted in the absence of *p*-TSA. The yield in this case was traced after 24 h. Obviously, *p*-TSA is an important component of the reaction.

In order to show the merits of *p*-TSA over other catalysts reported in the literature, results with this catalyst were compared with other catalysts utilized for the synthesis of α, α' -bis(substituted benzylidene) cycloalkanones. From Table 2, it can be seen that *p*-TSA appears to promote the reaction more effectively than a number of other catalysts, particularly in terms of the time and yield required to complete the reaction. This method offers some advantages in terms of low reaction times, simplicity of performance, solvent-free condition, low cost, and it follows along the line of green chemistry. The catalyst is readily available and inexpensive and can

conveniently be handled and removed from the reaction mixture.

In conclusion this paper describes efficient method for cross-Aldol condensation of aromatic aldehydes with cyclic ketones to form α, α' -bis(substituted benzylidene) cycloalkanones using *p*-TSA as a solid heterogeneous catalyst at 80°C under solvent-free conditions. The mild reaction conditions, shorter reaction times, high yields, and application of an inexpensive and readily available catalyst are the great advantages of the method.

Experimental

General procedure for the preparation of α, α' -bis(substituted benzylidene) cycloalkanones

A mixture of cycloalkanone **1** (5 mmol), aldehyde **2** (10 mmol), and *p*-TSA (1 mmol) was added to a round-bottomed flask equipped with a reflux condenser. The mixture was stirred at 80°C for an indicated time to complete the reaction monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was cooled to room temperature. Water (10 mL) was added and the mixture was stirred for 10 min in order to solve the catalyst. The obtained solid was collected by filtration to give, in many cases, the pure α, α' -bis(substituted benzylidene) cycloalkanones. In some cases, the aforementioned residue was purified by crystallization (EtOAc-EtOH) to afford pure products.

Selected spectral data

2,6-Dibenzylidene cyclohexanone (3a)

IR (KBr): 3072, 3023, 1658, 1570, 1445, 1271, 1415, 1271, 1145, 770 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): $\delta = 7.81$ (s, 2 H, =CH), 7.46–7.24 (m, 10H, ArH), 2.92 (t, 4H, *J* = 5.6 Hz, CH₂), 1.80–1.74 (m, 2H, CH₂).

2,6-Di(4-chlorobenzylidene)cyclohexanone (3b)

IR (KBr): 2927, 1664, 1608, 1579, 1270, 833 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): $\delta = 7.73$ (s, 2 H, =CH), 7.41–7.36 (m, 8H, ArH), 2.90 (t, 4H, *J* = 6.0 Hz, CH₂), 1.83–1.79 (m, 2H, CH₂).

2,6-Di(3-nitrobenzylidene)cyclohexanone (3c)

IR (KBr): 3108, 2928, 1669, 1591, 1514, 1490, 1343, 1267, 856 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): $\delta = 8.33$ (s, 2 H, =CH), 8.22 (d, 2H, *J* = 8.0 Hz, ArH), 7.81–7.60 (m, 6H, ArH), 2.98 (t, 4 H, *J* = 5.6Hz, CH₂), 1.90–1.84 (m, 2H, CH₂).

Table 1. Preparation of α,α' -bis(substituted benzylidene) cycloalkanone catalyzed by *p*-TSA at 80°C under solvent-free conditions.

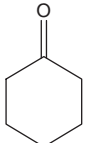
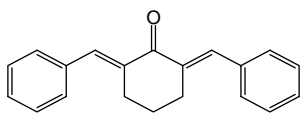
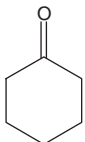
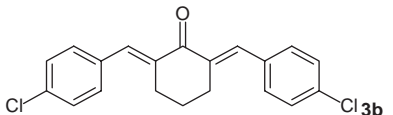
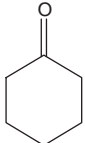
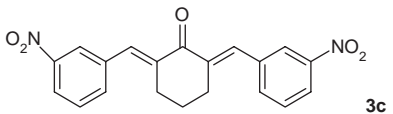
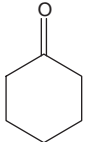
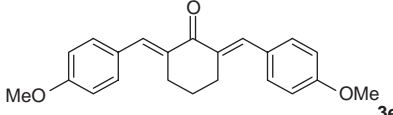
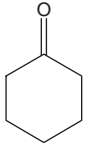
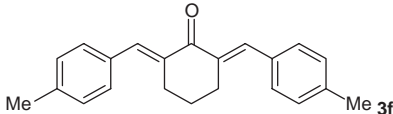
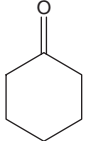
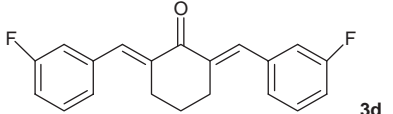
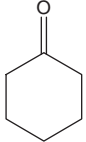
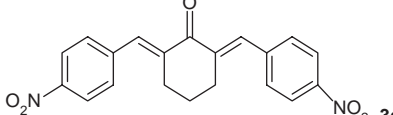
Entry	Cycloalkanone	Ar	Product	Time (min)	Yield (%) (<i>a</i>)	Mp (°C)	
						Found	Reported (<i>Ref.</i>)
1		C ₆ H ₅	 3a	20	75	116–118	116–118 (22)
2		4-ClC ₆ H ₄	 3b	10	98	146–148	146–148 (14)
3		3-NO ₂ C ₆ H ₄	 3c	5	84	188–190	188–189 (12)
4		4-MeOC ₆ H ₄	 3e	5	75	160–162	160–162 (23)
5		4-MeC ₆ H ₄	 3f	5	80	167–169	168 (24)
6		3-FC ₆ H ₄	 3d	15	80	88–89	88–89 (25)
7		4-NO ₂ C ₆ H ₄	 3g	5	82	203–204	159–160 (26)

Table 1 (Continued)

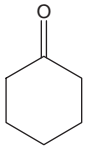
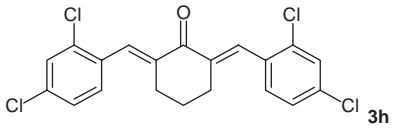
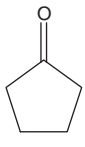
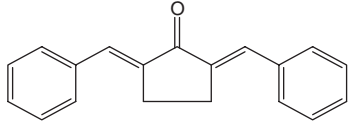
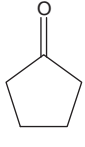
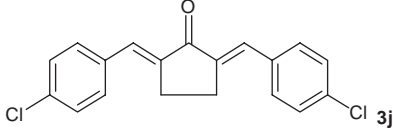

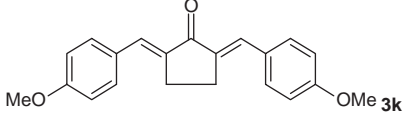
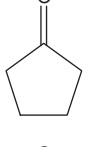
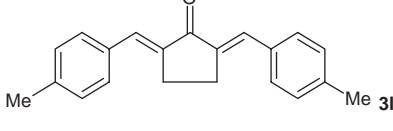
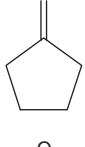
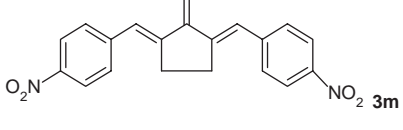
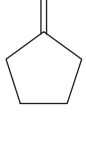
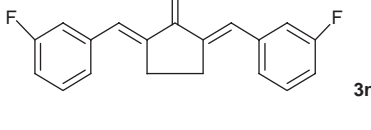
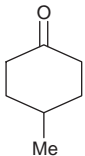
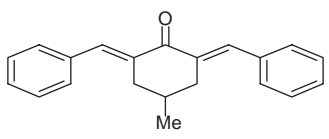
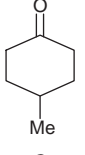
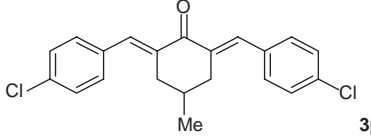
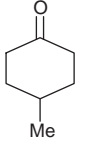
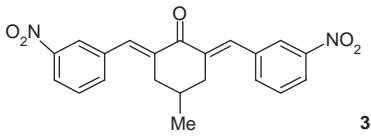
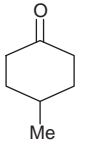
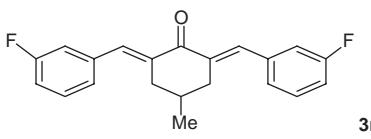
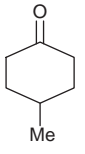
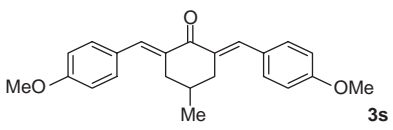
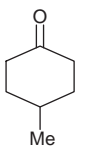
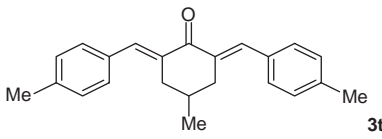
Entry	Cycloalkanone	Ar	Product	Time (min)	Yield (%) (<i>a</i>)	Mp (°C)	
						Found	Reported (<i>Ref.</i>)
8		2,4-Cl ₂ C ₆ H ₃	 3h	10	86	163–164	163–164 (<i>11</i>)
9		C ₆ H ₅	 3i	5	90	188–189	188–189 (<i>27</i>)
10		4-ClC ₆ H ₄	 3j	5	85	229–230	229–230 (<i>14</i>)
11		4-MeOC ₆ H ₄	 3k	5	80	214–216	214–216 (<i>14</i>)
12		4-MeC ₆ H ₄	 3l	10	85	243–244	243–244 (<i>11</i>)
13		4-NO ₂ C ₆ H ₄	 3m	5	86	253–254	230–231 (<i>12</i>)
14		3-FC ₆ H ₄	 3n	5	80	190–193	88–89 (<i>25</i>)

Table 1 (Continued)

Entry	Cycloalkanone	Ar	Product	Time (min)	Yield (%) (a)	Mp (°C)	
						Found	Reported (Ref.)
15		C ₆ H ₅	 3o	20	87	97–99	97–99 (27)
16		4-ClC ₆ H ₄	 3p	5	90	156–160	156–160 (27)
17		3-NO ₂ C ₆ H ₄	 3q	15	85	165–166	– (b)
18		3-FC ₆ H ₄	 3r	15	88	98–99	– (b)
19		4-MeOC ₆ H ₄	 3s	5	85	137–139	137–139 (27)
20		4-MeC ₆ H ₄	 3t	10	85	125–127	125–127 (27)

Note: (a) Isolated yields, (b) not reported.

Table 2. Comparison of results using *p*-TSA with other heterogeneous catalyst for synthesis of α,α' -bis(substituted benzylidene) cycloalkanones.

Entry	Catalyst	T (°C)	Time (h)	Yield (%)	Ref.
1	copper(II) trifluoroacetate	90	6	77–99	(1)
2	Cu(OTf) ₂	80	6–12	86–96	(12)
3	Silica sulfuric acid	80	2–3.5	86–97	(24)
4	KF/Al ₂ O ₃	35–40	0.5–2.5	60–96	(23)
5	Sulfonated Carbon Nanocage	70	0.5–2	72–92	(26)
6	<i>p</i> -TSA	80	5–20 min	75–98	This work

2,6-Di(3-fluorobenzylidene)cyclohexanone (3f)

IR (KBr): 2943, 1662, 1581, 1437, 1169, 1145, 783 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.76 (s, 2 H, =CH), 7.43–7.38 (m, 2H, ArH), 7.25 (d, 2H, *J* = 8.0 Hz, ArH), 7.19 (dd, 2H, *J* = 10 Hz, *J* = 2 Hz, ArH) 7.10–7.05 (m, 2H, ArH), 2.96–2.93 (m, 4 H, CH₂), 1.87–1.81 (m, 2H, CH₂).

2,5-Dibenzylidenecyclopentanone (3i)

IR (KBr): 3053, 3018, 1690, 1626, 1602 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.60–7.58 (m, 6H, ArH, and =CH), 7.45–7.36 (m, 6H, ArH), 3.13 (s, 4H, CH₂).

2,5-Di(4-methoxybenzylidene)cyclopentanone (3k)

IR (KBr): 3080, 2851, 1684, 1590 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.59 (d, 4H, *J* = 8.0 Hz, ArH), 7.58 (s, 2H, =CH), 6.98 (d, 4H, *J* = 8.0 Hz, ArH), 3.88 (s, 6H, OCH₃), 3.07 (s, 4H, CH₂).

2,5-Di(4-nitrobenzylidene)cyclopentanone (3m)

IR (KBr): 3105, 2843, 1706, 1605, 1522 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 8.32–8.30 (m, 4H, ArH), 7.76–7.65 (m, 6H, ArH, and =CH₂), 3.20 (s, 4H, CH₂)

2,5-Di(3-fluorobenzylidene)cyclopentanone (3n)

IR (KBr): 2943, 1668, 1601, 1441, 1169, 1210, 778 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.56 (s, 2 H, =CH), 7.46–7.38 (m, 4H, ArH), 7.33–7.29 (m, 2H, ArH) 7.14–7.10 (m, 2H, ArH), 3.14 (s, 4H, CH₂).

2,6-Di(3-nitrobenzylidene)4-methylcyclohexanone (3q)

IR(KBr): 2956, 1667, 1608, 1526, 1348, 1196, 1147, 891, 820, 748, 674 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 8.32 (s, 2H, =CH), 8.25–8.23 (m, 2H, ArH), 7.83 (s, 2 H, ArH), 7.78 (d, 2H, *J* = 8.0 Hz, ArH), 7.64 (t, 2H, *J* = 8.0 Hz, ArH), 3.05 (dd, 2H, *J* = 3.6 Hz, *J* = 3.6 Hz, CH₂), 2.66–2.58 (m, 2H, CH₂), 2.02–1.93 (m, 2H, CH), 1.13 (d, 3H, *J* = 6.4 Hz, CH₃). Anal.

calcd. for C₂₁H₁₈N₂O₅ (378.38): C, 66.66; H, 4.79; N, 7.40%. Found: C, 66.56; H, 4.65. N, 7.34%.

2,6-Di(3-fluorobenzylidene)4-methylcyclohexanone (3r)

IR(KBr): 2927, 1663, 1612, 1584, 1431, 1213, 1152, 1016, 784, 682 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.76 (s, 2 H, =CH), 7.43–7.38 (m, 2H, ArH), 7.29–7.25 (m, 2H, ArH), 7.19–7.17 (m, 2H, ArH), 7.10–7.05 (m, 2H, ArH), 3.06 (dd, 2H, *J* = 3.6 Hz, *J* = 3.6 Hz, CH₂) 2.57–2.50 (m, 2H, CH₂), 1.97–1.88 (m, 1H, CH), 1.12 (d, 3H, *J* = 6.8 Hz, CH₃). Anal. calcd. for C₂₁H₁₈F₂O (324.36): C, 77.76; H, 5.59%. Found: C, 77.61; H, 5.51%.

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