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Synthesis Of α,α′-Bis(Substituted Benzylidene)Cycloalkanones And Chalcones Catalyzed With p-Toluenesulfonic Acid (PTSA) On Montmorillonite K10 Under Solvent-Free Conditions

Corresponding Author

Mohammed M.Hashemi
Department of Chemistry, Sharif University of Technology, P.O.Box 11365-9516, Tehran, (IRAN)
Fax: 0098216005718
E-mail: mhashemi@sharif.edu

Co-Authors

Behzad Khalili, Bagher Eftekhari-Sis
Department of Chemistry, Sharif University of Technology, P.O.Box 11365-9516, Tehran, (IRAN)

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ABSTRACT

p-Toluenesulfonic acid (PTSA) on montmorillonite K10 efficiently catalyzes crossed aldol condensation of aromatic aldehydes with ketones under solvent-free conditions to afford the corresponding α,α′-bis(substituted benzylidene) cycloalkanones and chalcones in high yields without occurrence of any side reactions. This method is very general, simple and environmental friendly in contrast with the existing methods, which use many classical Lewis acids. Furthermore, the catalyst can be recycled for subsequent reactions without any appreciable loss of efficiency.

KEYWORDS

α,α′-Bis(substituted benzylidene)cycloalkanone;
Chalcones;
Crossed aldol condensation;
PTSA;
Montmorillonite K10;
Solvent-free conditions.

INTRODUCTION

The α,α′-bis(substituted benzylidene) cycloalkanones are very important precursors to potentially bioactive pyrimidine derivatives[1], intermediates of agrochemical, pharmaceuticals[2], and perfumes[3], new organic material for nonlinear optical applications[4], cytotoxic analogous[5], and the units of liquid-crystalline polymers[6]. In addition, these compounds undergo double 1,3-dipolar cycloaddition reaction[7], with azomwthyne ylides to give bis-spiropyrrolidines, which are often the central ring systems of numerous natural products[8].

The chalcones are very common in natural product chemistry[9]. For a structurally simple group of compounds, chalcones have displayed an impressive array of biological activities, among which anti-malarial[10], anti-protozoal[11], anti-inflammatory[12],

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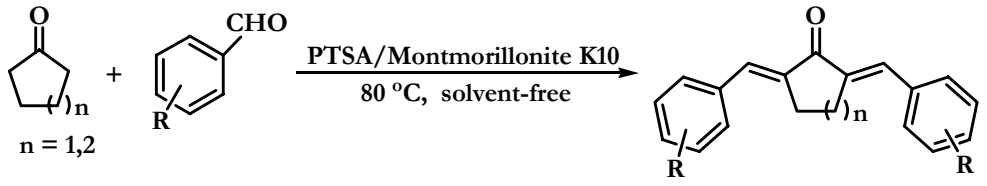

SCHEME 1

immunomodulatory[13], nitric oxide inhibition[14], tyronase inhibition[15], cytotoxic[16], and anticancer[17], activities have been cited in the literature.

The aldol condensation reaction is one of the versatile synthetic tools for construction of carbon-carbon bonds in organic chemistry[18]. Generally, benzylidenecycloalkanones and chalcones are prepared by cross aldol condensation of cycloalkanones with aldehydes in the presence of strong acid or bases. New and powerful variants of this classical reaction have been developed in the last 30 years. It has been reported that various complexes of metal(II) ions, such as Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) were used as catalysts[1a-c] but all the reported yields were less than 38%. In other case, bis(p-ethoxyphenyl) telluroxide (BOMPTO)[1d], $RuCl_3$[1f], SmI_3[19], Cp_2ZrH_2[20], Cp_2TiPh_2[21], $TiCl_3(SO_3CF_3)$[22], KF/Al_2O_3[23], $FeCl_3$[24], $BF_3{\cdot}OEt_2$,[25] and $InCl_3$[26], have also been used to catalyze the cross reaction. However, a good yield of products can only be obtained at high temperature and the purification operations are always complicated. It is, therefore, important to find a more convenient method for the preparations of these compounds.

PTSA is explored extensively in organic reactions such as cyclodehydration[27], oxidative α-tosyloxylation[28], protection of carbonyl group[29], conjugated addition of indole to chalcones[30], etc.

Synthetic chemists have been using highly dispersed mineral solids with extensive specific areas, for a considerable time. Many organic reactions have been devised in which the reagents are deposited on various inorganic solid supports. These reagents have advantages over the conventional homogeneous solution techniques: easy set-up and work-up, mild experimental conditions, high yields and/or selectivity[31]. Montmorillonite K10 had a great impact in organic synthesis and has offered major breakthroughs for the fine chemicals manufacturing industries[32].

As part of our research on chemical transformations[33], in this paper we report a simple and environmentally benign methodology for the crossed aldol condensation reaction under solvent-free conditions using PTSA on montmorillonite K10 as catalyst.

Different types of aldehydes were subjected to crossed aldol condensation reaction on the clay-supported PTSA. The overall reaction is as shown in (SCHEME 1).

EXPERIMENTAL

NMR spectra were recorded on a Bruker ACF 500. IR spectra were measured using a Perkin Elmer 781 spectrometer. CH_2Cl_2 was distilled before use.

Procedure for preparation of catalyst: PTSA (7g) was added to deionized water(100mL) and the mixture was stirred for 5 min until complete dissolution of the PTSA. Montmorillonite K10(20g) was then added. The resulting suspension was stirred vigorously for 2h. The solvent was evaporated and then the dry solid was placed in oven at 80°C for 3 h. 1 g of catalyst contains 0.14 g PTSA (2mmol).

General procedure for synthesis of α,α′-bis(substituted benzylidene) cycloalkanones and chalcones: Ketone(2mmol), aromatic aldehyde(4.2mmol) and PTSA/montmorillonite K10 (2 g, equal to 4 mmol of H+) were mixed thoroughly, placed in a glass tube and capped. The mixture was heated in an oven at 80°C for 2-3.5h (TABLE 1 and TABLE 2). After complete conversion of the ketone, as indicated by TLC, the mixture was cooled to room temperature. Dichloromethane(20-30mL) was added and heated for few minutes. The reagent was removed by filtration. The filtrate was concentrated and the solid residue was recrystallized from ethanol to afford the pure product. All compounds were characterized by their mp and spectroscopic data(IR, ^{1}HNMR) by comparison with those reported in the literature.

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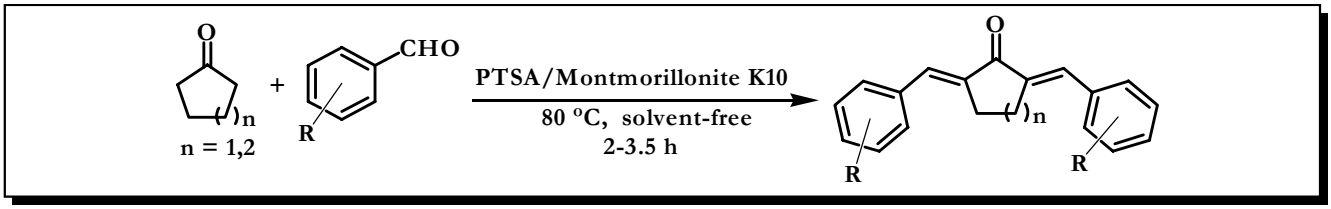
TABLE 1: Crossed aldol condensation of cycloalkanones with aromatic aldehydes



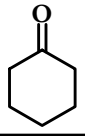
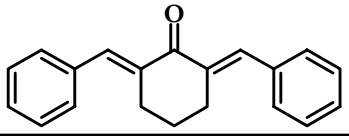
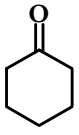
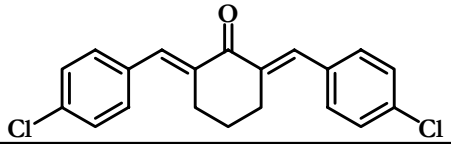
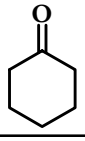
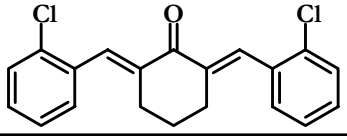
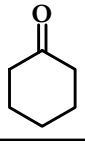
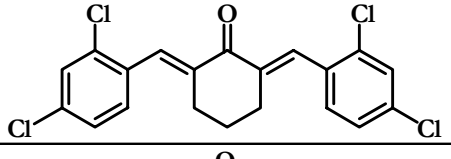
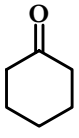
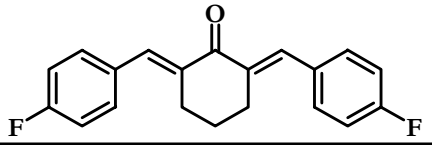
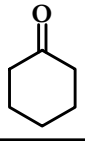
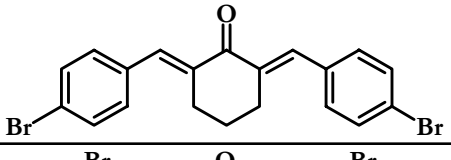
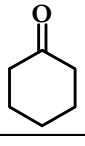
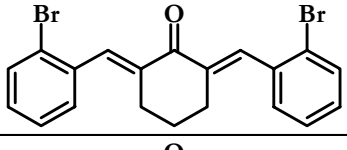
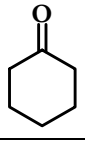
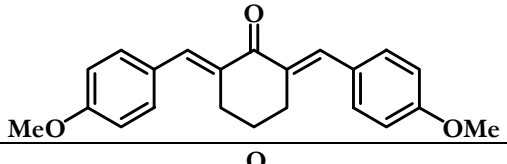
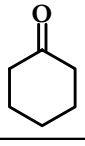
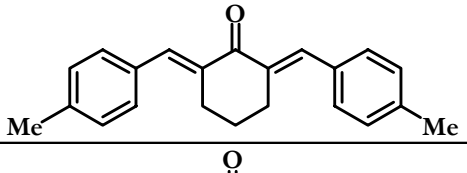
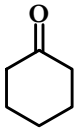
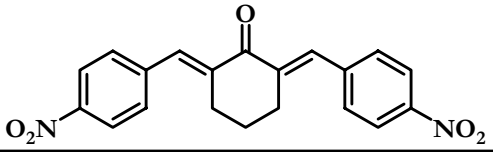
Entry	Ketone	Aldehyde	Product	Time (h)	Yield (%)[a]
1		C_6H_5CHO		2	90, 88, 87[b]
2		p-ClC_6H_4CHO		3.5	87
3		o-ClC_6H_4CHO		3.5	85
4		2,4-$Cl_2C_6H_3CHO$		3.5	85
5		p-FC_6H_4CHO		3.5	80
6		p-BrC_6H_4CHO		3.5	97
7		o-BrC_6H_4CHO		3.5	95
8		p-$MeOC_6H_4CHO$		3.5	94
9		p-MeC_6H_4CHO		3	79
10		p-$NO_2C_6H_4CHO$		3	87

TABLE 1: Continued

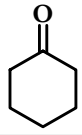
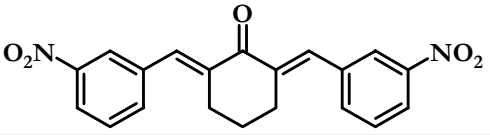
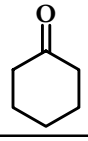
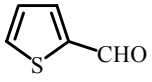
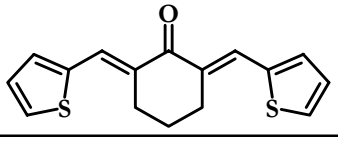
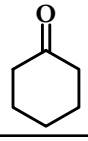
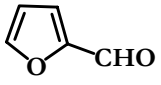
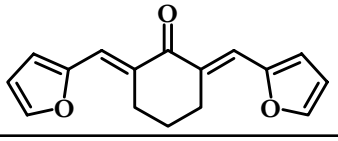
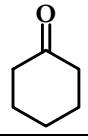
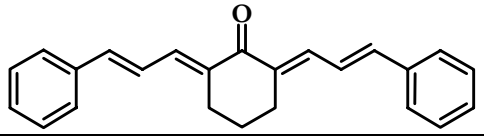
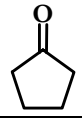
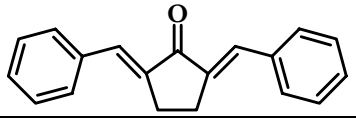
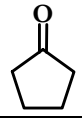
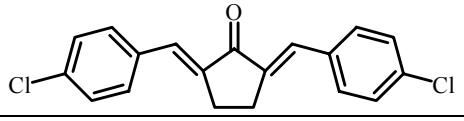
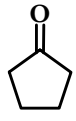
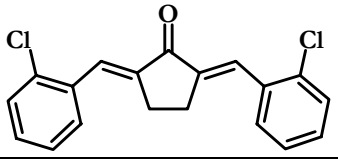
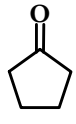
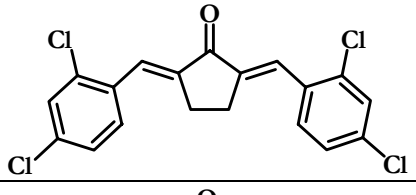
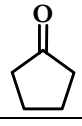
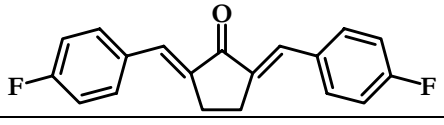
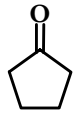
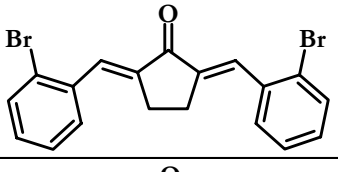
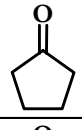
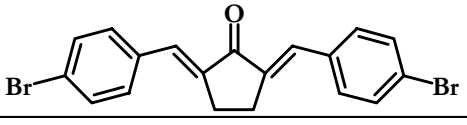
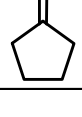
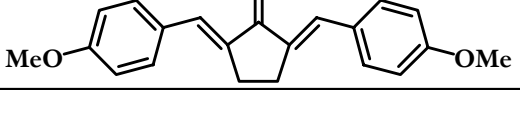
11		m-$NO_2C_6H_4CHO$		4	94
12				3	86
13				3	84
14		$C_6H_5CH=CHCHO$		3	96
15		C_6H_5CHO		2	95
16		p-ClC_6H_4CHO		2.5	98
17		o-ClC_6H_4CHO		2.5	96
18		2,4-$Cl_2C_6H_3CHO$		2.5	97
19		p-FC_6H_4CHO		2.5	91
20		o-BrC_6H_4CHO		3.5	97
21		p-BrC_6H_4CHO		2.5	98
22		p-$MeOC_6H_4CHO$		2.5	96

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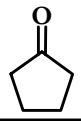
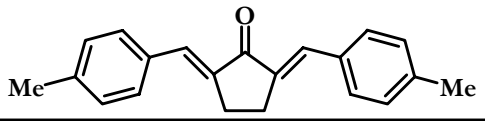
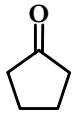
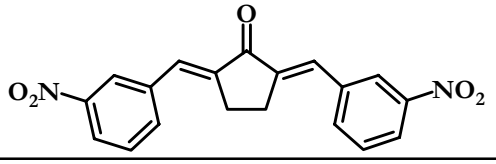
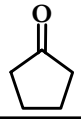
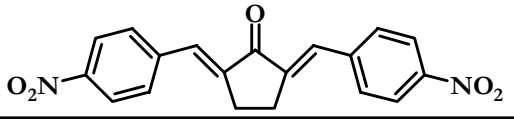
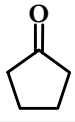
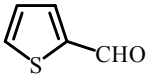
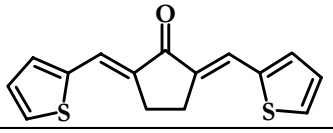
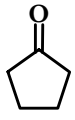
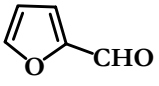
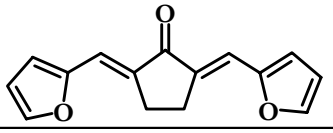
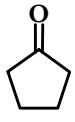
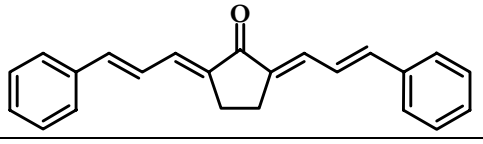
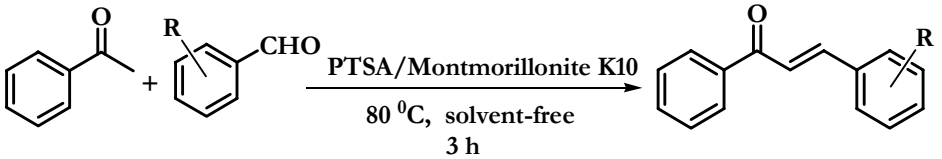
TABLE 1: Continued

23		p-MeC_6H_4CHO		2.5	89
24		m-$NO_2C_6H_4CHO$		3	98
25		p-$NO_2C_6H_4CHO$		2.5	98
26				2.5	91
27				2.5	88
28		$C_6H_5CH=CHCHO$		2.5	97

[a] All yields refer to isolated, all compounds identified with mp, IR and ^{1}HNMR spectroscopy.
[b] Catalyst was used over three runs.

TABLE 2: Aldol condensation of acetophenone with aldehydes



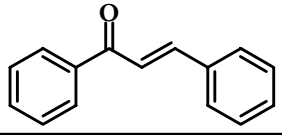
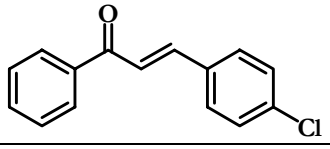
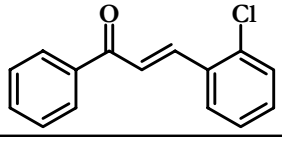
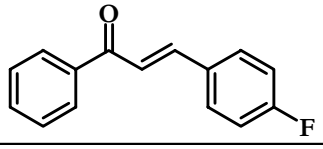
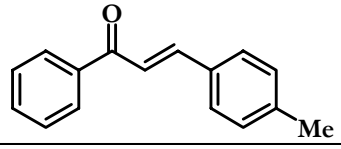
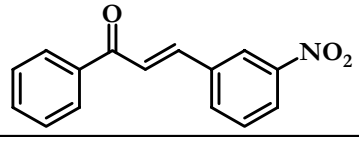
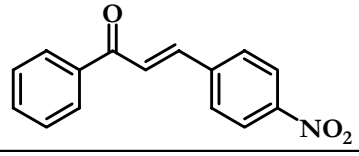
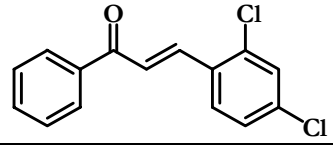
Entry	R	Product	Time (h)	Yield (%)[a]
1	H		3	94
2	p-Cl		3	98
3	o-Cl		3	95
4	p-F		3	98

TABLE 2: Continued

5	p-Me		3	97
6	m-NO_2		3	94
7	p-NO_2		3	98
8	2,4-Cl_2		3	92

RESULTS AND DISCUSSION

The results are summarized in the TABLE 1 and TABLE 2. The reactions were completed within 2-3.5h and high yields of α,α′-bis(substituted benzylidene) cycloalkanones and chalcones were obtained. Under these conditions, no self-condensation of the starting materials was observed. Attempted monocondensation from one side of cycloalkanones, in the presence of lower amounts of the aldehydes, was not successful.

Effect of catalyst on reaction(Time/Yield) was investigated using benzaldehyde with ketones for this purpose, as shown in TABLE 3, using of catalyst resulted in increased yield and decreasing of reaction time.

The catalyst could be recycled; entry 1, TABLE 1 describes the results of three consecutive reaction of benzaldehyde with cyclohexanone. In these experiments the product was isolated by filtration, the solid residues washed with dichloromethane, and the remaining catalyst reloaded with fresh reagents for further runs, follows reactivation(50°C, 2h). No decrease in the yield was observed demonstrating that PTSA/montmorillonite K10 can be reused as a catalyst in crossed aldol condensation.

TABLE 3: Effect of catalyst in reaction of ketones with benzaldehyde

Entry	Ketone	Time (h)/Yield (%)
1	Cyclohexanone	24/15[a], 6/35[b], 2/90[c]
2	Cyclopentanone	24/20[a], 6/42[b], 2/95[c]
3	Acetophenone	24/20[a], 6/40[b], 3/94[c]

[a] typical procedure without catalyst. [b]typical procedure with montmorillonite K10 instead of catalyst. [c]typical procedure

CONCLUSION

In conclusion, we have developed a very efficient and selective protocol for crossed-aldol condensation of ketones with aromatic aldehydes and high yield synthesis of α,α′-bis(substituted benzylidene) cycloalkanones and chalcones in the presence of a reusable and environmentally benign catalyst. Simple work-up procedure, including washing the mixture followed by evaporation of the solvent, is another advantage of this method.

2,6-Dibenzylidenecyclohexanone (TABLE 1. Entry 1)

mp 117-118°C. IR(KBr) υ:3024, 2926, 1657, 1609, 1570, 1440, 1268, 1144, 773 cm^{-1}·δ_H ($CDCl_3$, 500MHz) 7.81(2H, s), 7.33-7.48(10H, m), 2.96(4H, t, J=6.4 Hz,), 1.83-1.76(2H, m).

2,6-Bis-(4-chlorobenzylidene)-cyclohexanone (TABLE 1. Entry 2)

mp 146-148°C. IR(KBr) υ: 3050, 1690, 1583,

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1488, 981 cm^{-1}·δ_H ($CDCl_3$, 500MHz) 7.70(2H, s), 7.35-7.39(8H, m), 2.85(4H, t, J=5.6 Hz), 1.78-2.10 (2H, m).

2,6-Bis-(4-fluorobenzylidene)-cyclohexanone (TABLE 1. Entry 5)

mp 148-150°C. IR(KBr) υ:2929, 2910, 1661, 1601 cm^{-1}·δ_H ($CDCl_3$, 500MHz) 7.77(2H, s), 7.45-7.49(4H, m), 7.10-7.14(4H, m), 2.90-2.94(4H, m), 1.8-1.84(2H, m).

2,6-Bis-(4-methylbenzylidene)-cyclohexanone (TABLE 1. Entry 9)

mp 164-165°C. IR(KBr) υ: 2942, 2918, 1660, 1600 cm^{-1}·δ_H ($CDCl_3$, 500MHz) 7.78(2H, s), 7.18-7.39(8H, m), 2.92(4H, t, J=5.6 Hz), 2.39(6H, s) 1.75-1.79(2H, m).

2,5-Dibenzylidenecyclopentanone (TABLE 1. Entry 15)

mp 188-190°C. IR(KBr) υ: 3052, 3017, 2910, 1688, 1625, 1600 cm^{-1}·δ_H ($CDCl_3$, 500MHz) 7.58-7.60(6H, m), 7.35-7.45(6H, m), 3.12(4H, s).

2,6-Bis-(2-chlorobenzylidene)-cyclopentanone (TABLE 1. Entry 17)

mp 150-152°C. IR(KBr) υ:2922, 1697, 1600, 1518 cm^{-1}·δ_H ($CDCl_3$, 500MHz) 7.83(2H, s), 7.52-7.56(2H, m), 7.39-7.42(2H, m), 7.2-7.26(4H, m), 2.93(4H, s).

2,6-Bis-(4-nitrobenzylidene)-cyclopentanone (TABLE 1. Entry 25)

mp 229-231°C. IR(KBr) υ:3106, 2844, 1706, 1608, 1522 cm^{-1}·δ_H ($CDCl_3$, 500MHz) 8.30-8.32(4H, m), 7.65-7.76(6H, m), 3.21(4H, s).

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