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2-Aminoethanesulfonic acid immobilized on epichlorohydrin functionalized Fe₃O₄@WO₃ (Fe₃O₄@WO₃-EAE-SO₃H (III)): A heterogeneous and reusable nanocatalyst for synthesis of α,α'-bis (substituted-benzylidene) cycloalkanones in solvent-free conditions

Hanieh Karimzadegan, Batool Akhlaghinia*, Maryam Sadat Ghasemzadeh

Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad 9177948974, Iran.

ABSTRACT

A green, efficient, chemoselective, facile and clean procedure is described and discussed for the synthesis of α, α'-bis (substituted-benzylidene) cycloalkanones in solvent-free conditions. The condensation reaction was carried out through the reaction of aromatic aldehydes with cycloalkanones in the presence of Fe₃O₄@WO₃ (Fe₃O₄@WO₃-EAE-SO₃H (**III**)) nanoparticles as the catalyst. The nanostructured catalyst with the spherical shape, particle size in the range of 7-23 nm and superparamagnetic behavior may be referred as an excellent replacement for Brønsted acids. The reaction proceeds rapidly at room temperature, giving high yields of products. No self-condensation product was produced. Easy separation of the catalyst from the reaction mixture by means of an external magnetic field and re-using up to seven times without loss of activity are the salient features of the present method.

Keywords: α,α'-Bis (substituted-benzylidene) cycloalkanones, Aldehyde, Cycloalkanone.

1. Introduction

The α,α'-bis (substituted-benzylidene) cycloalkanones as important precursors of potentially bioactive pyrimidine derivatives [1], 2,7-disubstituted tropones [2], and synthetic intermediates to functionalize α,β-positions during the total synthesis of natural products such as cystodytins [3] have gained a lot of attention in organic synthesis. Additionally, they have intriguing biological activities such as antiangiogenic [4], quinine reductase inducer [5], cytotoxic [6], cholesterol-lowering activity [7] and large second-harmonic generation coefficient that is good enough for nonlinear optical materials [8].

Generally, crossed-aldol type condensation reaction of cycloalkanones with aldehydes with the aid of strong acids and more likely bases is available for the synthesis of these compounds [9-14]. Different catalysts including metal (II) ions [15], various reagents such as

Cp₂ZrH₂ [16], Cp₂TiPh₂ [17], BMPTO [18], RuCl₃ [19], SmI₃ [20], TiCl₃(CF₃SO₃) [21], La³⁺-immobilized organic solid [22], KF-Al₂O₃ [23], Mg(HSO₄)₂ [24], FeCl₃ [25] InCl₃ [26] TMSCl/NaI [27], TMSCl/Pd-C [28], SOCl₂ [29], Yb(OTf)₃ [30], K₂CO₃/PEG-400 [31], molecular I₂ [32], Et₃N in the presence of LiClO₄ [33], CaCl₂ as a Lewis base catalyst [34], acid-resins (A-15 and A-200C) in the presence of ultrasound irradiation [35], animal bone meal [36], alkoxy-bridged dinuclear Ti(IV) cluster [37], NaOAc [38], Cu(OTf)₂ [39], bromodimethylsulfonium bromide (BDMS) [40] and the microwave irradiation method [18] as well as ultrasound irradiation [41] have been used for this cross reaction. However, most of reported methods suffered from reverse and side reactions (self-condensation), long reaction times, high temperatures (120 °C) in sealed tubes under strict conditions and sometimes the produced water in the aldol-condensation reaction may hydrolyzed the catalyst. Considering the importance of α,α'-bis (substituted-benzylidene) cycloalkanones in synthetic organic chemistry and to improve the yield of reaction and also to reduce the reaction time, there is still

*Corresponding authors.
E-mail address: akhlaghinia@um.ac.ir (B. Akhlaghinia)

much scope to develop a new simple, efficient and clean catalytic method from the views of environmental and green chemistry. For these reasons and since our recent studies focused on developing green organic transformations [42-45] we sought to explore the preparation of α,α'-bis (substituted-benzylidene) cycloalkanones in the presence of a magnetically reusable solid supported heterogeneous catalyst through an effective, safe and eco-friendly chemical method. Very recently, we have demonstrated that Fe₃O₄@WO₃-EAE-SO₃H (**III**) nanoparticles as a nanostructured catalyst can be efficiently used for the preparation of 1-substituted-1*H*-1,2,3,4-tetrazoles that needs the use of an acidic catalyst [44].

To show the catalytic activity of Fe₃O₄@WO₃-EAE-SO₃H (**III**) nanoparticles further for another important transformation, the condensation reaction of aldehydes with cycloalkanones leading to the corresponding α,α'-bis (substituted-benzylidene) cycloalkanones in the presence of Fe₃O₄@WO₃-EAE-SO₃H (**III**) nanoparticles as a catalyst was investigated, we describe this herein (Scheme 1).

Fe₃O₄@WO₃-EAE-SO₃H (**III**) nanoparticles were prepared by the previously reported method in literature [44]. Briefly, The Fe₃O₄ MNPs were produced by coprecipitation of Fe (III) and Fe (II) in the alkaline solution. Subsequently, Fe₃O₄ MNPs were coated by WO₃ shell through the reaction with WCl₆, following oxidation at 420 ℃ to obtain Fe₃O₄@WO₃ (**I**). Next, Fe₃O₄@WO₃-E (**II**) was prepared by the reaction of Fe₃O₄@WO₃ (**I**) in pure epichlorohydrin at 60 ℃ with vigorous stirring. In the final step, Fe₃O₄@WO₃-EAE-SO₃H (**III**) was produced by treating II with 2-aminoethanesulfonic acid (taurine) in the NaOH solution.
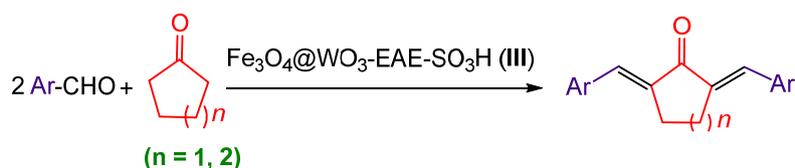
Scheme 1. Synthesis of α,α'-bis (substituted-benzylidene) cycloalkanones in the presence of Fe₃O₄@WO₃-EAE-SO₃H (**III**) nanoparticle.
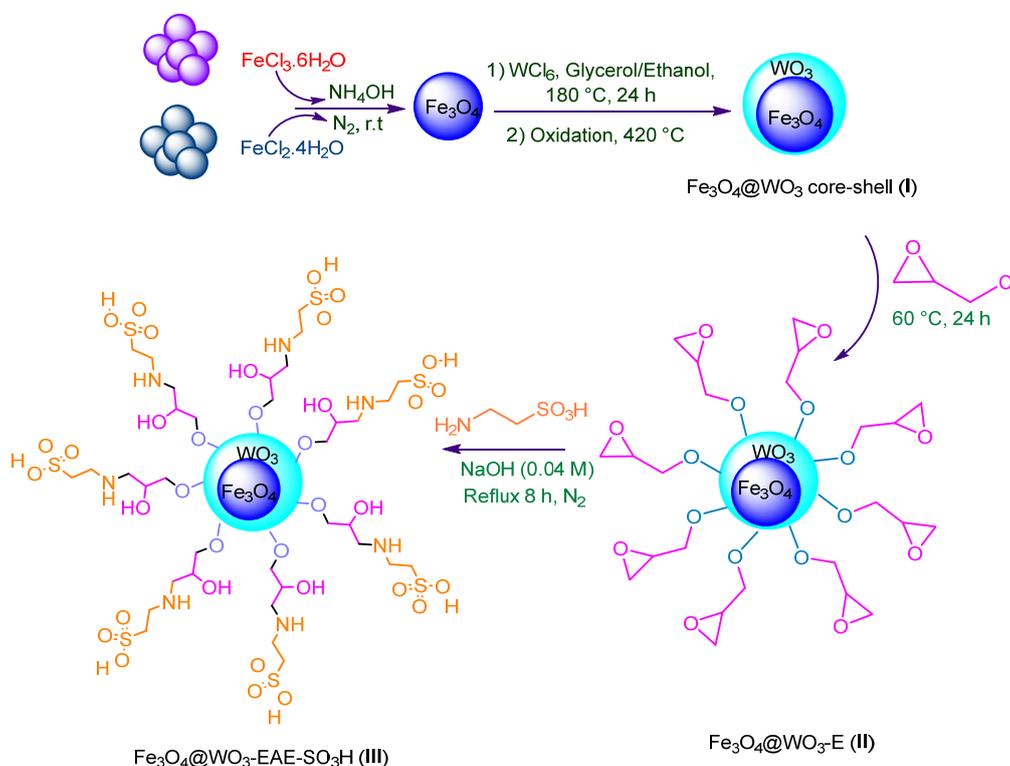
Scheme 2. An overview of the Fe₃O₄@WO₃-EAE-SO₃H (**III**) nanoparticles preparation.

2. Experimental

2.1. General

All chemical reagents and solvents were purchased from Merck and Sigma-Aldrich chemical companies and were used as received without further purification. The purity determinations of the products were accomplished by TLC on silica gel polygram STL G/UV 254 plates. The melting points of the products were determined with an Electrothermal Type 9100 melting point apparatus. The FT-IR spectra were recorded on an Avatar 370 FT-IR Therma Nicolet spectrometer. The NMR spectra were obtained in Brucker Avance 300 MHz instruments in $CDCl_3$. Mass spectra were recorded with a CH7A Varianmat Bremem instrument at 70 eV electron impact ionization, in *m/z* (rel %). All yields will be changed to isolated products after purification by recrystallization.

2.2. Preparation of magnetite nanoparticles (Fe₃O₄ NPs)

$FeCl_2.4H_2O$ (10 mmol, 1.99 g) and $FeCl_3.6H_2O$ (12 mmol, 3.25 g) were dissolved in deionized water (60 mL) under N_2 atmosphere at room temperature. Next, NH_4OH solution (0.6 M, 200 mL) was added to the stirring mixture at room temperature in order to reach the reaction pH of 11. The resulting black dispersion was stirred for 1 h at room temperature and then refluxed for 1 h to obtain a brown dispersion. Afterward, magnetic nanoparticles were separated with an external magnet, and then washed with deionized water. Finally, Fe_3O_4 NPs were dried at ambient temperature for 24 h.

2.3. Preparation of Fe₃O₄@WO₃ core-shell (I)

Under mild stirring, WCl_6 (0.5mmol, 0.198 g), ethylene glycol (20 mL) and Fe_3O_4 MNPs (1.5mmol, 0.346 g) were added to absolute ethanol (80 mL). Next, the resulting suspension was loaded in a Teflon-lined autoclave. After heating in 180 ℃ for 24 h, the suspension was cooled to room temperature. The final product was washed with ethanol and dried at 70 ℃ for 1 h. Afterwards, the $Fe_3O_4/W_{18}O_{49}$ was heated at 420 ℃ for 6 h to produce $Fe_3O_4@WO_3$ (**I**).

2.4. Preparation of epichlorohydrin functionalized Fe₃O₄@WO₃ (Fe₃O₄@WO₃-E) (II)

In 6 mL pure epichlorohydrin, $Fe_3O_4@WO_3$ (0.7 g) was added and dispersed by sonication for 30 min. Next, the suspension was heated at 60 ℃ for 24 h. The epichlorohydrin-functionalized $Fe_3O_4@WO_3$ was separated with a magnetic bar and then rinsed with MeOH (5 × 10 mL). The final products were dried at 40 ℃ for 14 h.

2.5. Preparation of 2-Aminoethanesulfonic acid immobilized on epichlorohydrin functionalized Fe₃O₄@WO₃ (Fe₃O₄@WO₃-EAE-SO₃H) (III)

Under N_2 atmosphere, $Fe_3O_4@WO_3$-E (**II**) (0.5 g) was added to a solution of 2-aminoethanesulfonic acid (5mmol, 0.7 g) in refluxing NaOH (0.04 M, 30 mL) for 8 h. Next, the resulting $Fe_3O_4@WO_3$- EAE-SO_3H (**III**) was separated with a magnet bar and washed to pH <7.5 with deionized water. Afterwards, the final products were dried at 60 ℃ for 24 h.

2.6. Typical procedure for synthesis of 2,6-di((E)-benzylidene) cyclohexan-1-one in the presence of Fe₃O₄@WO₃-EAE-SO₃H (III) (1a)

A mixture of cyclohexanone (1 mmol, 0.098 g), benzaldehyde (2 mmol, 0.212 g) and $Fe_3O_4@WO_3$-EAE-SO_3H (**III**) (0.01g) was stirred at room temperature under solvent-free conditions. Completion of the reaction was tested by TLC. After completion of the reaction, ethyl acetate (3 mL) was added to the solidified mixture and the magnetic insoluble catalyst was separated by an external magnetic field. Then the resulting solution was washed several times with distilled water (3×3 mL). Afterwards, the extracted organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated to get the product. 2,6-di((E)-benzylidene) cyclohexan-1-one was obtained in its yellowish crystalline form by recrystallization from ethanol (0.523 g, 90 %).

3. Results and Discussion

3.1. Catalytic synthesis of α,α'-bis (substituted-benzylidene) cycloalkanones in the presence of Fe₃O₄@WO₃-EAE-SO₃H (III) nanoparticles

During our ongoing studies on the development of efficient green synthetic methodologies [42-45,46-51] herein, we reported a new and simple synthesis of α,α'-bis (substituted-benzylidene) cycloalkanones *via* the crossed-aldol condensation reaction using $Fe_3O_4@WO_3$-EAE-SO_3H (**III**) nanoparticles. To optimize the reaction conditions at first, cyclohexanone and benzaldehyde were chosen as model substrates. In a set of experiments, the optimal conditions were established by varying the amount of the catalyst and solvent at room temperature. The results are presented in Table 1. The control experiment clarified that a very low yield of condensation product could be obtained in the absence of catalyst and also in the absence of solvent even after being stirred for 1 day (Table 1, entry 1). At the same reaction conditions different amounts of $Fe_3O_4@WO_3$-EAE-SO_3H (**III**) nanoparticles (0.008g, 0.01g and 0.02g) were examined to find the best yield

Table 1. Optimization of various reaction parameters for the preparation of 2,6-di((*E*)-benzylidene) cyclohexan-1-one.

Entry	Amount of catalyst (g)	Solvent	Temp. (°C)	Time (min)	Isolated Yield (%)
1	-	-	r.t	24(h)	5
2	0.008	-	r.t	15	85
3	**0.01**	**-**	**r.t**	**10**	**90**
4	0.02	-	r.t	10	90
5	0.01	H_2O	r.t	24 (h)	30
6	0.01	DMF	r.t	24 (h)	70
7	0.01	1,4-Dioxane	r.t	24 (h)	35
8	0.01	CH_3CN	r.t	24 (h)	10
9	0.01	EtOH	r.t	24 (h)	50
10	0.01	PEG	r.t	24 (h)	25
11	0.01	DMSO	r.t	24 (h)	50
12	0.01	THF	r.t	24 (h)	33
13[a]	0.01	-	r.t	24 (h)	10
14[b]	0.01	-	r.t	24 (h)	15
15[c]	0.01	-	r.t	24 (h)	35
16[d]	0.01	-	r.t	24 (h)	75

[a]The reaction was performed in the presence of Fe_3O_4 NPs.
[b]The reaction was performed in the presence of $Fe_3O_4@WO_3$.
[c]The reaction was performed in the presence of $Fe_3O_4@WO_3$ -E.
[d]The reaction was performed in the presence of 2-aminoethanesulfonic acid (taurine).

of desired product. As shown in Table 1, the best result in terms of economy and reaction time was obtained when 0.01 g of catalyst was used (Table 1, entries 2-4). Under similar conditions, further studies were carried out on the effect of different solvents (H_2O, DMF, 1,4-dioxane, CH_3CN, EtOH, PEG, DMSO and THF) on the model reaction. To ensure complete conversion, after relatively long reaction times (24 h), we found that the product yield was obviously depressed (Table 1, entries 5-12). To monitor whether the use of $Fe_3O_4@WO_3$-EAE-SO_3H (**III**) nanoparticles, is crucial for this transformation under the optimized reaction conditions, the model reaction was also conducted in the presence of Fe_3O_4 NPs, $Fe_3O_4@WO_3$ (**I**), $Fe_3O_4@WO_3$-E (**II**) and 2-aminoethanesulfonic acid (taurine) respectively (Table 1, entries 13-16). It is evident from the obtained results that $Fe_3O_4@WO_3$-EAE-SO_3H (**III**) nanoparticles has a vital catalytic activity in the present condensation reaction.

Using the optimized reaction conditions (Table 1, entry 3), we next extended the approach on the reaction of a series of electronically modified aromatic aldehydes with cyclohexanone or cyclopentanone to prepare α,α'-bis (substituted-benzylidene) cycloalkanones in the presence of $Fe_3O_4@WO_3$-EAE-SO_3H (**III**)

nanoparticles (Table 2) and discussed the generality, scope and limitation of the proposed synthetic methodology. Under these conditions all reactions completed rapidly at room temperature and excellent yields of desired products were obtained within 5-40 min without any mono-aldol (α-mono (substituted benzylidene) cycloalkanone) and ketones self-condensation products whereas, product mixtures were normally observed in classical reaction conditions [16]. Using 1 : 1 or even less mole ratio of cyclohexanone /or cyclopentanone to aldehyde does not afford the above-mentioned by-products.

The results presented in Table 2 show that the condensation reaction of aldehydes with cyclohexanone proceeded more quickly than the condensation reaction of aldehydes with cyclopentanone (entries 1-10 *vs.* entries 11-20). Also, electron rich aldehydes favor the formation of products (Table 2 entries 2, 3, 14, 15), while electron-withdrawing groups (such as Br, Cl, F and NO_2) at the phenyl ring of aldehydes decrease the reaction rate slightly (Table 2, entries 5-9 and 17-21). In spite of electron releasing effect of -OH, 2-hydroxy benzaldehyde reacts with cyclohexanone and cyclopentanone in 17 and 24 min respectively due to steric effect of -OH group in *ortho* position.

Table 2. Synthesis of different structurally α,α'-bis (substituted-benzylidene) cycloalkanones in the presence of Fe_3O_4@WO_3-EAE-SO_3H (**III**) nanoparticles.

Entry	Ar	n	Product	Time (min)	Isolated Yield (%)	m.p. (°C)	Ref.
1	C_6H_5	2	**1a**	10	90	119-121	[61]
2	4-Me-C_6H_4	2	**1b**	8	95	166-168	[61]
3	4-MeO-C_6H_4	2	**1c**	5	95	160-162	[61]
4	2-OH-C_6H_4	2	**1d**	17	90	146-149	[65]
5	3-Br-C_6H_4	2	**1e**	18	90	111-112	[66]
6	4-Cl-C_6H_4	2	**1f**	15	95	148-151	[61]
7	2-Cl-C_6H_4	2	**1g**	22	90	101-104	[61]
8	4-F-C_6H_4	2	**1h**	20	90	155-158	[61]
9	4-O_2N-C_6H_4	2	**1i**	30	95	161-163	[39]
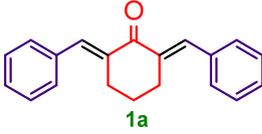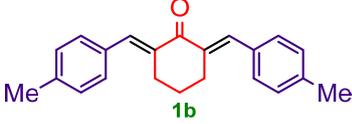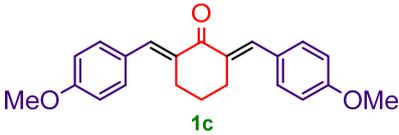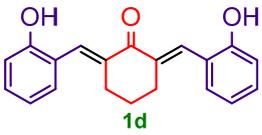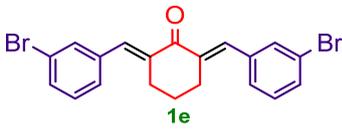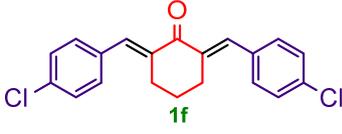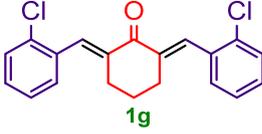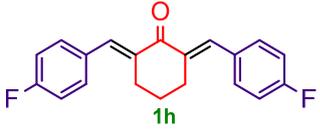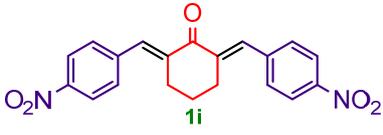
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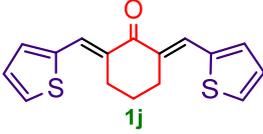
10	2-C₄H₄S	2	**1j**	28	90	141-143	[29]
12	2-C₄H₄O	2	**1k**	30	95	141-142	[38]
12	4-C₅H₅N	2	**1l**	25	90	148-149	[63]
13	C₆H₅	1	**1m**	30	90	188-190	[61]
14	4-Me-C₆H₄	1	**1n**	25	95	240-243	[61]
15	4-MeO-C₆H₄	1	**1o**	20	95	210-212	[29]
16	2-OH-C₆H₄	1	**1p**	24	90	180-182	[67]
17	3-Br-C₆H₄	1	**1q**	20	90	212-214	[54]
18	4-Cl-C₆H₄	1	**1r**	25	90	226-229	[61]
19	2-Cl-C₆H₄	1	**1s**	32	90	154-156	[61]
20	4-F-C₆H₄	1	**1t**	35	90	206-208	[61]
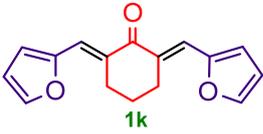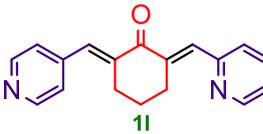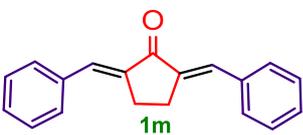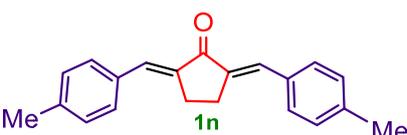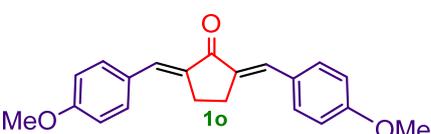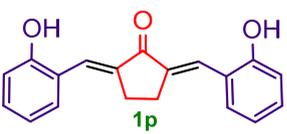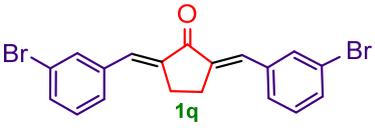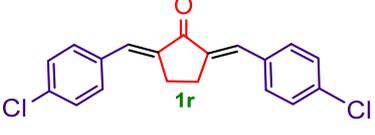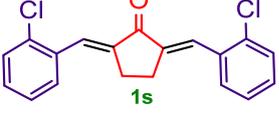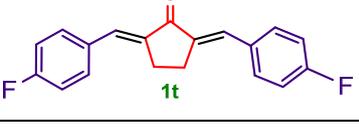
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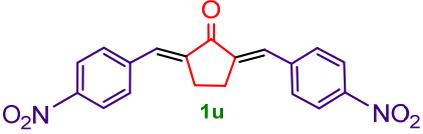
21	4-O$_2$N-C$_6$H$_4$	1	1u	40	90	232-233	[39]
22	2-C$_4$H$_4$S	1	1v	30	95	221-223	[64]
23	2-C$_4$H$_4$O	1	1w	32	95	167-168	[39]
24	4-C$_5$H$_5$N	1	1x	25	90	167-168	[63]
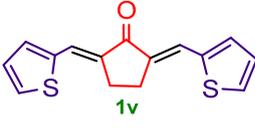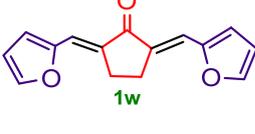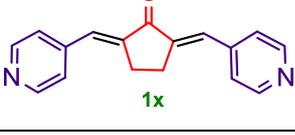
Difference in reactivity between *ortho*-substituted aromatic rings and *para*-substituted ones can be rationalized by the steric effects (entry 6 *vs.* entry 7 and entry 18 *vs.* entry 19). The present system was further examined for the condensation reaction of heteroaromatic aldehydes with cyclohexanone /or cyclopentanone in the presence of Fe$_3$O$_4$@WO$_3$-EAE-SO$_3$H (**III**) nanoparticles under the optimized reaction conditions. Comparatively, heteroaromatic aldehydes undergo this reaction with equal efficiency (Table 2, entries 10-12 and entries 22-24). It was also found that the condensation reaction cannot be carried out if aliphatic aldehyde is used.

All the condensation products were known and isolated, purified and initially characterized by comparison of their melting points with the reported values. Mass spectrometry confirmed the molecular weights of all products as well. Furthermore, the structures of some selected compounds (**a**, **b**, **f**, **j**, **k** and **m**) were deduced from their high-field ^{1}HNMR, ^{13}CNMR and FT-IR spectral data. Results showed that the reactions were clean and no side-reactions were observed. Based on earlier literature reports and ^{1}H NMR data, the chemical shifts of vinyl protons of all synthesized α,α'-bis (substituted-benzylidene) cycloalkanones appeared as a singlet in the region of 7.62-8.02 ppm. The downfield shifting indicates a strong anisotropic effect resulting from the close proximity of the vinylic protons to the carbonyl groups and overlapping of the vinylic protons with the aromatic protons as well. Thus, inspection of ^{1}H NMR data clearly indicated that the

α,α'-bis (substituted-benzylidene) cycloalkanones were obtained purely in the *EE* geometry of the double bonds as the sole products [52-54]. Other resonating signals at about 2-4, 7-7.5 ppm are allocated to aliphatic and aromatic protons respectively. The characteristic signals in the ^{13}CNMR spectra corroborate the chemical structures of α,α'-bis (substituted-benzylidene) cycloalkanones. The spectra include signals around 189-196 and 136-139 ppm which are corresponded to carbonyl and olefinic carbons. *(See the supporting information file for details)*

Additionally, to evaluate the stereo-chemistry of the present method, detailed study was examined for a selected compound (**1j**) based on an extensive ^{1}H NMR experiment involving the NOESY technique. As can be seen in Fig. 1a, there is not any NOE between H$_4$ (vinylic protons at *δ* 7.9 ppm) and H$_3$ (methylene protons at C-3 (*δ* 2.9 ppm)). Also, Fig. 1b showed the NOE of the vinylic protons (H$_4$) with the aromatic *ortho* protons in thienyl ring (see the magnified red cycle in Fig. 1b).

In accordance with previous reports in literature for acid catalyzed condensation reactions [55], preparation of α,α'-bis (substituted-benzylidene) cycloalkanones in the presence of Fe$_3$O$_4$@WO$_3$-EAE-SO$_3$H (**III**) nanoparticles follows the same mechanism (Scheme 3). The catalytic activity of Fe$_3$O$_4$@WO$_3$-EAE-SO$_3$H (**III**) nanoparticles in preparation ofα, α'-bis (substituted-benzylidene) cycloalkanones was established by conducting the model reaction without a catalyst and also in the presence of Fe$_3$O$_4$ NPs, Fe$_3$O$_4$@WO$_3$ (**I**) NPs,
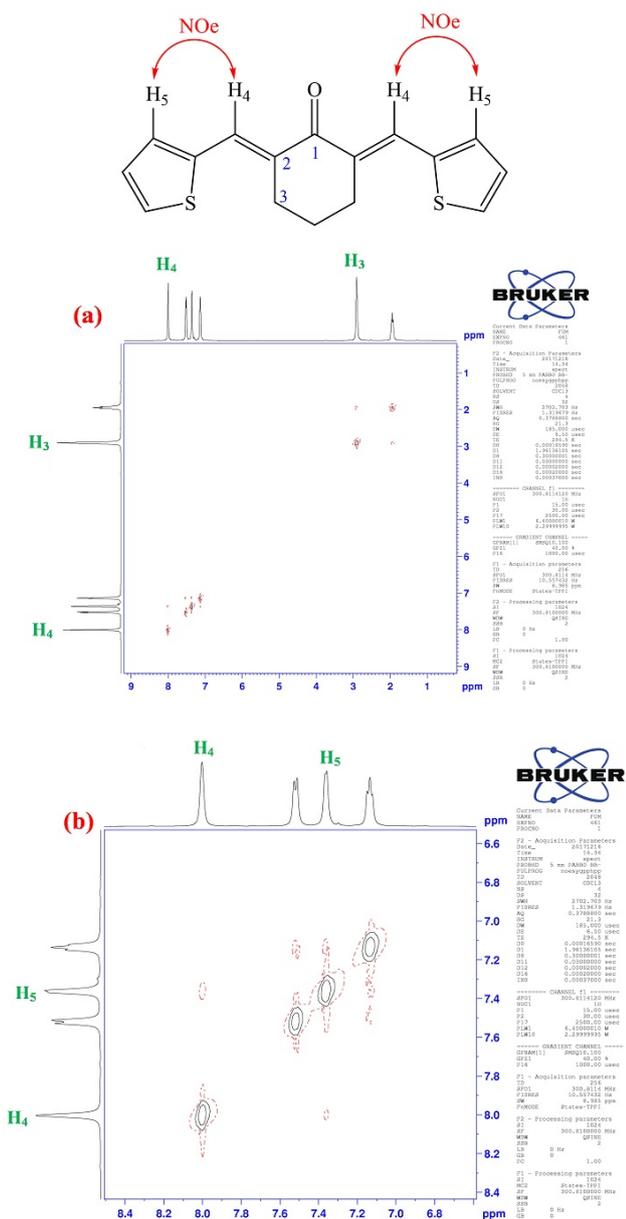
Fig. 1. H-H NOESY spectrum of (2*E*,6*E*)-2,6-bis(thiophen-2-ylmethylene) cyclohexan-1-one (1j).

and Fe₃O₄@WO₃-E (**II**). It is evident from Table 1, entries 1 and 13-16 that the reasonable yields of target compound were not obtained even after long period of time. It is assumed that the reaction is initiated by tautomerization of cycloalkanone and protonation of carbonyl functionality of non-enolizable aromatic aldehyde in acidic media. Thus, the nucleophilic attack of enol form **I'** on protonated aldehyde **II** which leads to the formation of intermediate **III** is facilitated. In the next step, protonation of **III** which is followed by dehydration affords the carbocationic intermediate **V**. Rapid deprotonation of carbocationic intermediate **V** from the α-carbon of the cycloalkanone leads to

formation of α-mono (substituted benzylidene) cycloalkanone **VI**. Enolization of **VI** as an α,β-unsaturated ketone generates **VI** which upon nucleophilic attack on protonated non-enolizable aromatic aldehyde generates **VII** (as the reaction is carried out in the ratio (non-enolizable aromatic aldehyde/cycloalkanone) of 2 : 1).α,α'-bis (substituted-benzylidene) cycloalkanones **X** as the final resultant product is obtained through protonation of **VII**, followed by dehydration of **VIII** and deprotonation process of **IX** respectively. Thereafter, the solid acid nanocatalyst is released and re-enters to the catalytic cycle for further turnovers. Further studies are being carried out to elucidate the detailed mechanism.

Based on the results obtained from Table 1 and the proposed mechanism in Scheme 3, the condensation reaction of cyclohexanone with aromatic aldehydes was completed faster than the reaction of cyclopentanone. Moreover, it is evident from Table 2 that non-enolizable aromatic aldehydes with electron releasing groups were condensed more quickly compared with aldehydes bearing electron withdrawing groups. More electron releasing leads to easier formation of carbocationic intermediate **V** and **IX**. It means that enolization step and carbocation formation may be referred to as effective steps in the reaction rate. (Angel strain in cyclopentanone caused more difficult formation of corresponding enol form than cyclohexanone which has an enol form free of any angle strain). To testify the selectivity of the reaction, we carried out the model reaction by applying 1: 1 molar ratio of benzaldehyde: cyclohexanone. Interestingly, it was observed that only α-mono((*E*)-2-benzylidenecyclohexan-1-one) cyclohexanone was produced exclusively.

From the perspective of 'green chemistry', regeneration and re-use of the catalyst is highly desirable. Thus, the study of the recovery and re-use of Fe₃O₄@WO₃-EAE-SO₃H (**III**) nanoparticles as a heterogeneous magnetic catalyst was carried out for the condensation of cyclohexanone with benzaldehyde under the conditions mentioned (Table 1, entry 3). As the quantity of the catalyst used was too low to collect again and be reused after the first run, to investigate its reusability, the higher quantity of the catalyst was taken. Hence the model reaction was carried out by using 0.01 g of Fe₃O₄@WO₃-EAE-SO₃H (**III**) nanoparticles and the experiments were properly scaled up. After each run, the magnetic nanocatalyst was removed simply by a magnetic field, washed with hot ethyl acetate, dried at 60 ℃ for 2 h and reused in the next run. Fig. 2 demonstrated that the recycled and reused Fe₃O₄@WO₃-EAE-SO₃H (**III**) nanoparticles showed the same catalytic activity as a fresh catalyst without
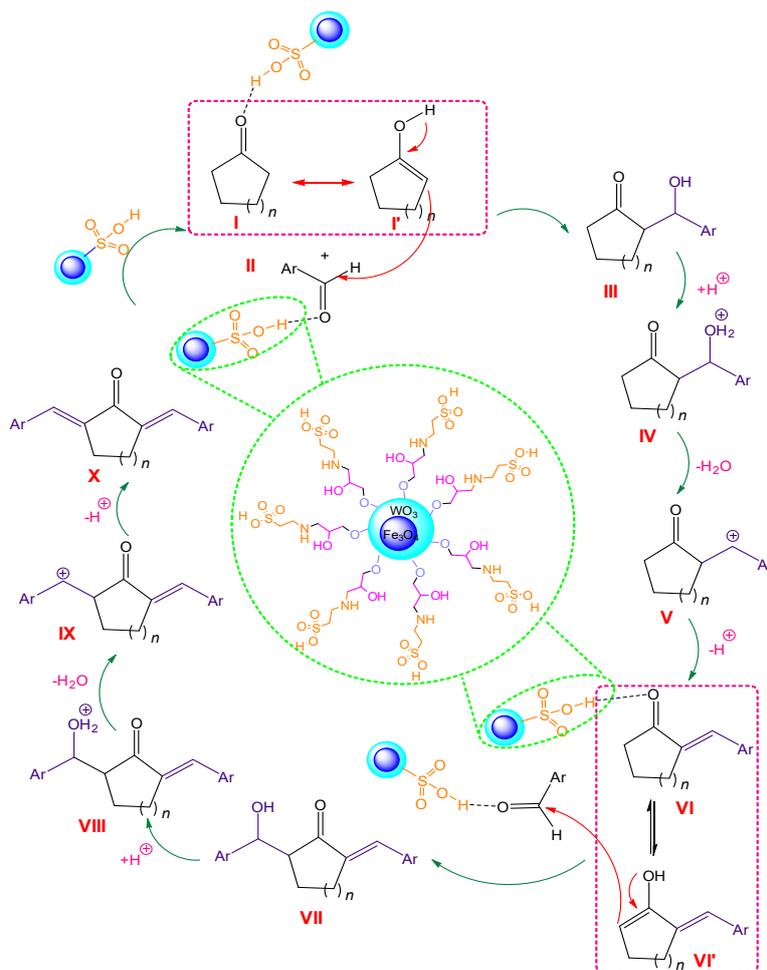
Scheme 3. Proposed reaction mechanism for the synthesis of α,α'-bis (substituted-benzylidene) cycloalkanones in the presence of Fe₃O₄@WO₃-EAE-SO₃H (**III**) nanoparticles.

attenuated activity and a minimal decrease in conversion and the isolated yield was observed after seven runs. The model reaction proceeded with 100/90%, 100/90%, 100/90%,94/85%, 94/85%,88/80%, 88/80% conversion/isolated yield after seven successive cycles (Fig. 2).

Consequently, a reduction in the activity of Fe₃O₄@WO₃-EAE-SO₃H (**III**) might be due to the chemisorption of species on catalytic sites; likewise, the deactivation of nanocatalyst might be caused by the physical deposit of reactants onto the nanocatalyst surface or in the nanocatalyst pores [56].
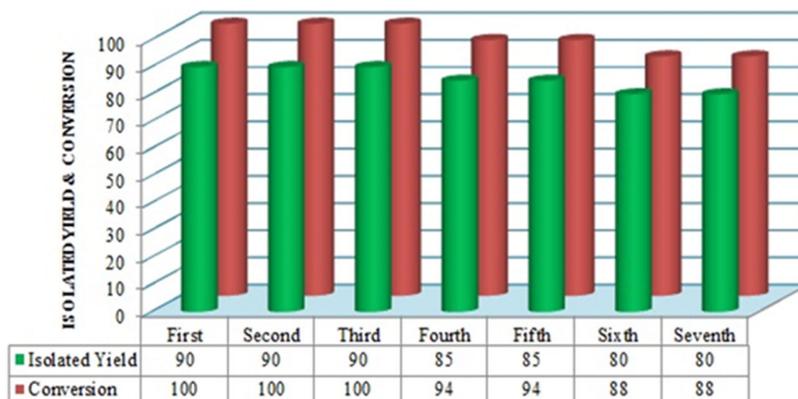
Fig. 2. Synthesis of 2,6-di((*E*)-benzylidene) cyclohexan-1-one in the presence of the reused Fe₃O₄@WO₃-EAE-SO₃H (**III**) nanoparticles.

Back-titration analysis of the 7th reused Fe_3O_4@WO_3-EAE-SO_3H (**III**) nanoparticles revealed that the amount of loaded -$NHCH_2CH_2SO_3H$ per 1.000 g of nanocatalyst was decreased to 0.185 mmol. The result clearly indicates that 4% of active acidic sites (negligible amount) leached out during seven catalytic reaction runs (fresh catalyst contains 0.225 mmol of -$NHCH_2CH_2SO_3H$ per 1.000 g).

To obtain deeper insight into the efficacy and general applicability of Fe_3O_4@WO_3-EAE-SO_3H (**III**) nanoparticles for the synthesis of α, α'-bis (substituted-benzylidene) cycloalkanones, the results obtained by the present study were compared with some of those reported previously (Table 3). In comparison, as is evident from Table 3, although each of these methods has their own advantages, none of them can provide magnetically separation of the catalyst from the reaction mixture. Additionally, long reaction times to achieve reasonable yield (Table 3, entries 1, 4-6, 8-9, 11-13), higher temperatures (Table 3, entries 1, 4, 6, 8, 11-17), using expensive and environmentally hazardous catalysts and solvents (Table 3, entries 1, 5, 6, 9, 10, 13) are the other drawbacks of most of the reported methods.

4. Conclusions

In conclusion, a general and efficient synthetic method for preparation ofα, α'-bis(substituted-benzylidene) cycloalkanones using Fe_3O_4@WO_3-EAE-SO_3H (**III**) nanoparticles was achieved. The reaction can be carried out at room temperature under solvent free conditions and follows the mechanism of acid-catalyzed condensation. The shorter reaction times, milder reaction conditions, improved product yields, simple work-up procedures, greater ease of purification, and easy recovery as well as reuse of this nanostructured catalyst are the main superiorities of the present catalytic system which are expected to contribute to the development of more benign synthetic methods. We believe that the scope and generality of the present methodology as an attractive addition to the existing methods in the literature will find wide applications in organic synthesis.

Acknowledgements

Table 3. Comparison between efficiency of Fe_3O_4@WO_3-EAE-SO_3H (**III**) and some other catalysts for the synthesis of 2,6-di((*E*)- benzylidene) cyclohexan-1-one.

Entry	Catalyst	Solvent	Temp. (°C)	Time	Yield (%)	Ref.
1	Yb(OPf)$_3$[a]	$C_{10}F_{18}$	120	8(h)	97	[57]
2	Na-HAP	-	Mw	4(min)	86	[58]
3	TiO_2-P25-SO_4^{2-}	-	Mw	2(min)	99	[59]
4	$ZrCl_4$	EtOH	reflux	5(h)	95	[60]
5	TMSCl/NaI	CH_3CN	r.t	60(min)	95	[27]
6	Yb(OTf)$_3$	-	90	6(h)	94	[30]
7	KF-Al_2O_3	-	Mw	5(min)	83	[61]
8	$InCl_3$.4H_2O	-	110	6(h)	95	[26]
9	KF/Al_2O_3	MeOH	30-35	40(min)	89	[41]
10	BDMS[b]	-	r.t	4(min)	98	[40]
11	Cu(OTf)$_2$	-	80	6(h)	95	[39]
12	NaOAc	HOAc	120	7(h)	86	[38]
13	Alkoxy-bridged dinuclear Ti(IV) cluster	Toluene	80	13(h)	97.8	[37]
14	Na/ABM[c]	H_2O	reflux	20(min)	96	[36]
15	*n*-TSA[d]	-	90	20(min)	93	[62]
16	$Cs_1H_2PW_{12}O_{40}$	-	50	10(min)	98	[63]
17	Fe_3O_4@WO_3-EAE-SO_3H (**III**)	-	r.t	10(min)	90	This work

[a]Ytterbium perfluorooctane sulfonate.
[b]BDMS: Bromodimethylsulfonium bromid.
[c]ABM: Animal bone meal.
[d]*n*-TSA: Nano titania supported sulfonic acid.

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