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FULL PAPER

Direct oxidative esterification of toluene with 1,3-dicarbonyl compounds catalysed by copper complex supported on magnetic nanoparticles

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Funding information Tarbiat Modares University Toluene oxidation is one of the substantial industrial technologies since oxidized products are industrially very important intermediates. A Fe₃O₄@cysteine@Cucatalysed reaction that uses *tert*-butyl hydroperoxide as oxidant to produce esters from toluene and β -diketones or β -keto esters, enolate precursors, has been developed. Oxidative esterification of toluene with 1,3-dicarbonyl derivatives led to C–O bond formation and direct C–H functionalization.

KEYWORDS

esterification, magnetic, nanoparticles, oxidation, toluene

1 | **INTRODUCTION**

The ester moiety is among the most abundant functional groups in natural products, polymers, fine chemicals, bulk chemicals and pharmaceuticals.^[11] Traditionally, esters are often prepared by the nucleophilic addition of an alcohol to activated carboxylic acid derivatives such as acid anhydrides or chlorides.^[2] Further efforts have been devoted to the direct synthesis of esters using Steglich esterification,^[3] Mitsunobu reaction^[4] and Baeyer–Villiger oxidation.^[5] However, because of several reaction steps, production of unwanted by-products, poor atom economy and difficulty of product isolation in all of the above three methods, it is one of the challenges of green and sustainable chemistry to update these old processes.

The selective oxidation of C–H bonds is of fundamental and technological importance, from biological and industrial chemistry viewpoints.^[6] C–H bonds are omnipresent in nature and thus the capability for selective C–H bond functionalization is of considerable interest to chemists.^[7] A rapidly increasing number of new organic reactions based on C–H cleavage have been developed.^[11] Many of new bond have been formed through this efficient way, including carbon–carbon^[2] and carbon–heteroatom^[3] bond formation.^[8]

One of the crucial methods of activation for passive row material is selective oxidation of primary carbon–hydrogen bonds to form intermediates and final products.^[9]

Volatile organic compounds can lead to serious environmental problems. Catalytic oxidation is an effective way for reducing the distribution of these compounds.^[10]

Toluene as the simplest member of the alkyl aromatics is one of the inactive row materials that can be oxidized to benzyl alcohol, benzaldehyde, benzoic acid and benzyl benzoate. Khan et al. reported the benzylation of aromatic carboxylic acids with toluene in the presence of NaBrO₃/ NaHSO₃.^[11] After the pioneering work reported by Fu and co-workers where Bu₄NI was used for oxidative esterification of alcohols with toluene,^[12] subsequently, Zhang and coworkers described Pd(II)-catalysed benzylation of carboxylic acids with toluene.^[13] In 2012, ZhiPing and co-workers reported oxidative C–C bond formation from benzylation of 1,3-dicarbonyl compounds with simple toluene derivatives. Fe-activated 1,3-dicarbonyl compound and reduced peroxide thus improved hydrogen abstraction from the benzylic C–H bond.^[14]

This motivated us to repeat the reaction in the presence of a magnetic catalyst and we found that this catalyst could construct C–O bonds through oxidative coupling of toluene with 1,3-dicarbonyl compounds. Heating a mixture of methylacetoacetate, 4 eq. of oxidant *tert*-butyl hydroperoxide (TBHP; 70% aqueous solution) and 10 mg of catalyst in toluene gave 25% yield of enol ester and no benzylation of 1,3-dicarbonyl compound product (Scheme 1).



SCHEME 1 Oxidative coupling of toluene with 1,3-dicarbonyl compounds

Yoo and Li reported CuBr-catalysed oxidative esterification of aldehydes with β -dicarbonyl compounds.^[15] Although direct transformations of aldehydes into esters have been reported, a one-pot procedure that integrates oxidation of toluene and CO bond formation into a single operation has not been published. Examples of oxidative coupling are shown in Scheme 2.

Recently, we have described a hypervalent iodine-catalysed oxidative amidation in which the sp³-hybridized C–H bond was oxidized adjacent to an amine in the presence of oxidant which then can be functionalized with a variety of heteroatoms.^[16] We found that toluene undergoes stereoselective transformation to enol esters in the presence of a 1,3-dicarbonyl compound, 20 mol% of Fe₃O₄@cysteine@Cu and 4 eq. of TBHP.

Heterogeneous catalysts are usually preferred over homogeneous catalysts; in addition to easily separation from a reaction mixture, heterogeneous catalysts can be used in flow reactors.^[17] To oxidize toluene, copper-based binary metal oxides,^[18] phenyl modification of Mn-containing mesoporous silica,^[19] CoSBA-15^[20] and Au–Pd alloy nanoparticles^[9] have been used to find a most suitable oxidation catalyst but all of these showed low turnover numbers.

L-Cysteine (Cys) is a semi-essential α -amino acid with a thiol side chain. Its carboxylic acid group facilitates the easy



SCHEME 2 Representative oxidative coupling of arylmethane with ketones

linkage of the amino acid to a magnetite support and the amino and thiol side chains render it suitable to serve as a complexing agent for most of transition metal ions. Among transition metals, copper is of considerable interest. It is found normally with oxidation states of +1 or +2 which can be stabilized depending on the nature of ligands, counter ion and solvent. So interconversion of these oxidation states makes copper suitable to serve as a catalyst for oxidation reactions. Furthermore, copper shows advantages of being cost effective and comparatively safe for biological organisms.

In extension to our recent work,^[21] we have now prepared a new catalyst consisting of a Cys–copper acetate complex supported on magnetic nanoparticles (NPs). This catalyst is very effective and has several advantages such as being cost effective, high yielding, involving shorter reaction times, no by-product formation and most importantly its easy usage with negligible reduction in catalytic activity.

A major advantage of the direct oxidative esterification of toluene approach is that it provides efficient fast access to enol esters under mild conditions, while isolation of the catalyst is also easy.

Modification of a magnetic surface with Cys is an effective method to increase the catalytic activity of Cu in the oxidation of toluene. The conversion was improved when Cu was complexed with Cys. This organic modification strategy of magnetic NPs could also be useful for easy separation of catalyst from reaction mixture.

2 | RESULTS AND DISCUSSION

The prepared heterogeneous catalyst was characterized using Fourier transform infrared (FT-IR) spectroscopy, scanning electron microscopy (SEM), powder X-ray diffraction (XRD), thermogravimetric/differential thermal analysis (TG/ DTA), vibrating sample magnetometry (VSM), inductively coupled plasma atomic emission spectroscopy and energydispersive X-ray (EDX) analysis.

The crystalline structure of Fe₃O₄@Cys@Cu NPs and phase purity were determined using powder XRD as shown in Figure 1. The XRD pattern of magnetic NPs is indexed to the spinel phases of iron oxide and six peaks $(2\theta = 30.1^{\circ}, 35.5^{\circ}, 43.2^{\circ}, 53.5^{\circ}, 57.0^{\circ} \text{ and } 62.8^{\circ})$ are related to their corresponding indices (220), (311), (400), (422), (511) and (440), respectively.

For investigating the surface, morphology and size of NPs, we used SEM. The resulting image (Figure 2) shows uniform and minuscule NPs. The approximate size of the particles is determined to be about 30–50 nm.

The TG technique is very helpful to understand the degradation temperatures, moisture content and percentage of inorganic and organic components in a material. Figure 3 shows the TG analysis of Fe₃O₄@Cys@Cu NPs, indicating that around 7.5% of the Cys gets disintegrated between 200 and 500 °C. The weight loss of the NPs below 200 °C can



FIGURE 1 XRD pattern of Fe₃O₄@Cys@Cu NPs



FIGURE 2 SEM image Fe₃O₄@Cys@Cu NPs



FIGURE 3 TG/DTA of Fe₃O₄@Cys@Cu NPs

be assigned to the release of physically adsorbed solvent and organic groups.

In order to deduce the composition of the NPs, EDX analysis was carried out (Figure 4). The EDX spectrum



FIGURE 4 EDX pattern of Fe₃O₄@Cys@Cu NPs

depicts no other peaks except those for Fe₃O₄@Cys@Cu NPs (Fe, Cu, S, C, N, O) indicating the high purity of thecomposite. The results of this analysis for the Fe₃O₄@Cys@Cu NPs are summarized in Table 1. The elemental compositions of magnetic Fe₃O₄@Cys@Cu NPs are (%): 0.43 (C), 0.20 (N), 4.24 (O), 0.53 (S), 1.22 (Cu) and 93.38 (Fe) (Table 1). This implies that Cys@Cu complex is on the surface of Fe₃O₄ NPs.

Bare nanocrystals of Fe₃O₄ have high saturation magnetization of 73.7 emu g⁻¹ at room temperature.^[24] The result of VSM (Figure 5) shows that the saturation magnetization value of Fe₃O₄@Cys@Cu (55 emu g⁻¹) is lower than that of Fe₃O₄ NPs due to the coating of the Cys@Cu complex.

The FT-IR spectra of magnetic NPs (Fe_3O_4), Cys and magnetic NPs coated by Cys ($Fe_3O_4@Cys$) are shown in

 TABLE 1
 Weight percent of various elements on the surface of Fe₃O₄@Cys@Cu NPs from EDX analysis

Element	Line	Intensity	Wt%
С	Ka	28.2	0.43
Ν	Ka	14.6	0.20
0	Ka	820.2	4.24
S	Ka	131.2	0.53
Fe	Ka	2167.3	93.38
Cu	La	72.1	1.22 (0.31 mmol g^{-1})
			100.00



FIGURE 5 Magnetization curve of Fe₃O₄@Cys@Cu NPs

Figure 6. The FT-IR spectrum of Cys is characterized by the following absorption bands: NH₂ and OH arising at 3431 cm⁻¹ as a broad band and carbonyl group at 1739 cm⁻¹. Compared with the FT-IR spectrum of Fe₃O₄, the presence of Cys covers the vibration of Fe₃O₄. The band shift of the C=O bending vibration from 1739 to 1705 cm⁻¹ is significant. This phenomenon indicates that the O from CO coordinates with Fe on the surface of the magnetite nanocrystals. The spectrum of the Fe₃O₄@Cys@Cu catalyst shows a characteristic band at 1630 cm⁻¹ (C=O) and a broad band with a shoulder at 569 cm⁻¹ is assigned to the formation of Cu complex.



FIGURE 6 FT-IR spectra

TABLE 2 Optimization of reaction condition	FABLE 2	Optimization	of reaction	conditions
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2.1 | Catalytic performance

We began our study with selective toluene oxidation in the presence of $Cu(OAc)_2$. Although $Cu(OAc)_2$ led to aldehyde (35%) using TBHP as oxidant, interestingly, the conversion was improved when Fe₃O₄@Cys-Cu(OAc)₂ was used in the reaction (52%). While this procedure has been demonstrated to be useful for toluene oxidation to aldehyde, it could be used for coupling reactions.

In an initial attempt, the reaction of toluene (3 ml) and methylacetoacetate (1 mmol) in the presence of heterogeneous catalyst (10 mg) with TBHP as oxidant (30% in water, 4 eq.) was performed at 80 °C. Enol ester was produced in low yield (25%). Key results of optimization of conditions are summarized in Table 2. Evaluation was initially examined with toluene and 1,3-dicarbonyl as starting materials, with a series of oxidants such as TBHP, H2O2 and mchloroperoxybenzoic acid (mCPBA) and solvents like dimethylsulfoxide (DMSO), acetonitrile, tetrahydrofuran (THF) and dioxane. The results show that mixed solvent acetonitrile-toluene (4:1 v/v) is effective in increasing the yield. No reaction occurs in the absence of oxidant and only 10% yield of enol ester is observed using TBHP without catalyst (Table 2, entries 17 and 18). Subsequently, the role of temperature was investigated. We find that 100 °C gives the best result for this reaction. Control experiments indicate that acetonitrile-toluene solvent and TBHP as oxidant are essential for achieving a high level of transformation (Table 2, entry 14). In the next step, the amount of catalyst was also optimized. Indeed, desired product is formed in the presence of

$R^{1} \xrightarrow{O} R^{2} \xrightarrow{Cu(II), Oxidant}_{CH_{3}CN/Toluene} \xrightarrow{R^{1}} R^{2} \xrightarrow{R^{2}}$									
Entry	Catalyst amount (mg)	Oxidant	Solvent	Temp. (°C)	Yield (%)				
1	10	TBHP	Toluene	80	25				
2	10	TBHP	THF-toluene (4/1)	80	25				
3	10	TBHP	DMSO-toluene (4/1)	80	5				
4	10	TBHP	Dioxane-toluene (4/1)	80	20				
5	10	TBHP	Acetonitrile-toluene (4/1)	80	40				
6	10	TBHP	Acetonitrile-toluene (4/1)	25	5				
7	10	TBHP	Acetonitrile-toluene (4/1)	40	20				
8	10	TBHP	Acetonitrile-toluene (4/1)	60	35				
9	10	TBHP	Acetonitrile-toluene (4/1)	100	60				
10	10	mCPBA	Acetonitrile-toluene (4/1)	100	10				
11	10	H_2O_2	Acetonitrile-toluene (4/1)	100	25				
12	10	UHP	Acetonitrile-toluene (4/1)	100	35				
13	5	TBHP	Acetonitrile-toluene (4/1)	100	15				
14	15	TBHP	Acetonitrile-toluene (4/1)	100	65				
15	20	ТВНР	Acetonitrile-toluene (4/1)	100	75				
16	25	TBHP	Acetonitrile-toluene (4/1)	100	75				
17	—	TBHP	Acetonitrile-toluene (4/1)	100	<10				
18	10	—	Acetonitrile-toluene (4/1)	100	ND				



SCHEME 3 Scope of reaction with respect to dicarbonyl compound substrates

20 mg of catalyst (Table 2, entry 15). Thus the optimal reaction conditions are considered to include toluene (3 ml), acetonitrile (1 ml), 1,3-dicarbonyl (1 mmol) and TBHP (4 mmol) at 100 $^{\circ}$ C for 24 h.



With optimal conditions in hand, we investigated the scope of 1,3-dicarbonyls (Scheme 3). Oxidative esterification using dimedone was not successful, while enol ester was produced when 2,4-pentanedione as another cyclic β -diketone was used, showing moderate yield.

To probe the details of the mechanism, a series of control experiments were designed and performed. When using hydroquinone as a radical scavenger, the reaction is completely inhibited. As outlined in Scheme 4, the suggested esterification reaction occurs through a sequential oxidation: (1) oxidation of toluene to alcohol; (2) oxidation of alcohol to aldehyde; (3) oxidative coupling of aldehyde with 1,3-dicarbonyl compound (Scheme 4).

The reusability of the catalyst was also evaluated. After accomplishing the reaction, the superparamagnetic nanocatalyst was separated from the medium with application of an external magnet, then washed and dried under vacuum at room temperature for 12 h, and used for the next reaction. The catalyst could be reused at least six times without any significant loss of the catalytic activity (Figure 7). Also, there is no change in the structure of the catalyst after the reaction: all of the observed XRD peaks are the same as the recorded pattern of primary catalyst (Figure 8).

3 | EXPERIMENTAL

All purchased solvents and chemicals were of analytical grade and used without further purification. FT-IR spectra





FIGURE 7 Activity lost as a function of number of reuse cycles of the catalyst



FIGURE 8 XRD pattern of reused catalyst after sixth run

were obtained over the range 400–4000 cm⁻¹ with Nicolet IR100 FT-IR with spectroscopic grade KBr. Powder XRD patterns were recorded at room temperature with a Philips X-Pert 1710 diffractometer using Co K α (λ = 1.78897 Å) at 40 kV and 40 mA. The data were collected from 10° to 90° (2 θ) with a scan speed of 0.02° s⁻¹. The morphology of the catalyst was studied using SEM (Philips XL 30 and S-4160) with gold coating equipped with EDX facility. The magnetic properties of the Fe₃O₄@Cys@Cu NPs were measured with a vibrating sample magnetometer/alternating

gradient force magnetometer (MDK Co., Iran, www.mdk-magnetic.com). TG/DTA was performed using a thermal analyser with a heating rate of 20 °C min⁻¹ over a temperature range of 25–1100 °C under flowing compressed nitrogen.

3.1 | Synthesis of magnetic catalyst

3.1.1 | Preparation of Fe₃O₄ coated with Cys

Amounts of 5 mmol of FeCl₃·6H₂O and 2.5 mmol of FeCl₂·4H₂O salts were dissolved in 100 ml of deionized water under vigorous stirring. Then 30 ml of NH₄OH solution (25%, w/w) and Cys (1 mmol) were added to the mixture until the pH was raised to 11 at which a black suspension was formed, followed by refluxing for 24 h. The residue was collected using a magnet, and washed several times with water and then ethanol to obtain Fe₃O₄@Cys.

3.1.2 | Immobilization of Fe₃O₄@Cys@Cu

An amount of 2 mmol of $Cu(OAc)_2 \cdot 2H_2O$ in 50 ml of water was added to Fe₃O₄@Cys NPs and stirred at room temperature for 24 h (Scheme 5). Finally, NPs were separated from the aqueous solution by magnetic decantation, washed with water and ethanol several times before being dried in an oven overnight.

3.2 | General procedure for oxidative esterification catalysed by Fe₃O₄@Cy@Cu(II)

To a mixture of catalyst (20 mol%) and 3 ml of toluene was added TBHP (2 mmol) as the oxidant. The mixture was magnetically stirred for 4 h at 100 °C. Then 1,3-dicarbonyl (1 mmol) and TBHP (70 wt% in water, 2 mmol) were added. The progress of the reaction was monitored by TLC. After the completion of the reaction, the catalyst was separated using an external magnet. Then, HCl (1 N, 5 ml) and EtOAc (5 ml) were added to the residual mixture and washed with NaHCO₃ (10 ml) and brine and dried over anhydrous Na₂SO₄. The organic layer was concentrated under reduced



pressure. The pure product was obtained after column purification using EtOAc and *n*-hexane.

4 | CONCLUSIONS

A robust and effective $Fe_3O_4@Cys@Cu(II)$ catalyst for oxidative esterification of a variety of 1,3-dicarbonyls was discovered and studied. When TBHP was used as an oxidant, oxidative esterification can be carried out to afford desired products in good yields. So, we have reported this new catalyst system which proves to be very effective.

It involves a simple procedure and is environmentally friendly and also incorporates special features like reagent economy, easy work-up and easy handling. Recovery of the catalyst was simple using an external magnet, allowing its reuse without significant loss of its catalytic activity (over six cycles).

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SUPPORTING INFORMATION

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