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Synthesis of *ortho*-Hydroxybenzophenones Catalyzed by Magnetically Retrievable Fe₃O₄ Nanoparticles under Ligand-Free Conditions

Thekkathu Ramani,*^[a] Paspulati Umadevi,^[a] K. Leon Prasanth,*^[b] and Bojja Sreedhar*^[a]

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ortho-Benzoylation of phenols with aryl aldehydes to afford the substituted 2-hydroxybenzophenones can be catalyzed efficiently by Fe₃O₄ nanoparticles under ligand-free conditions. This method is useful for the preparation of xanthones

Introduction

ortho-Hydroxybenzophenones are prevalent motifs in numerous natural products^[1] and in biologically active pharmaceuticals.^[2] They have been used as light stabilizers, UV absorbers in cosmetics and textiles, and as antianaphylactin in medicines.^[3] The most promising methods for their synthesis include Friedel-Crafts acvlation and esterification (O-acylation) of phenols followed by Fries rearrangement.^[4] However, these methods often suffer from harsh reaction conditions and require the handling of air-/water-sensitive Lewis acids; moreover, the reactions result in the formation of a mixture of (ortho and para) products, the separation of which is complicated.^[5] To circumvent these drawbacks, various alternative methods have been developed in which transition-metal-catalyzed cross-coupling reactions provide an excellent way to convert a C-H bond into C-O,^[6] C-N^[7] C-X^[8] C-S^[9] and C-C bonds.^[10] Recently, remarkable efforts were made in cross-dehydrogenative coupling (CDC) reactions and oxidative cross-coupling reactions by utilizing two different hydrocarbons as the reagents in a green, atom-economic, and sustainable manner.^[11] The development of highly efficient and selective catalytic systems in the oxidative coupling of an aldehyde C-H bond with other C-H bonds, and especially the unprotected C_{sp²}-H bonds in phenols, is still a great challenge, as simple phenols

[a] Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology Hyderabad 500607, India

E-mail: ramaniiict@gmail.com sreedharb@iict.res.in

- Homepage: www.iictindia.org [b] Department of Chemistry, The Zamorin's Guruvayurappan College, Calicut 673014, India
- E-mail: leonprasanthk@gmail.com
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are not suitable substrates because of the formation of unfavorable four-membered metallacycles.^[12] In this context, Miura and co-workers showed the benzoylation reaction of unprotected 1-naphthol by using aldehydes as benzoylating agents for the first time. They synthesized 2-benzoyl-1naphthol in the presence of $Pd(OAc)_2$ as the catalyst and PPh₃ as the ligand.^[13] Later, the Wang group reported the ortho-benzoylation of phenols with arenecarbaldehydes by using CuCl₂ as a catalyst in combination with PPh₃ as the ligand under basic conditions.^[14] Although the above results are promising, for eco-friendly reasons, it is necessary to develop a ligand-free and reusable catalytic system for the synthesis of *o*-hydroxybenzophenones.

Magnetic nanoparticles have been widely used as heterogeneous catalysts in various organic transformations. Among the various magnetic nanoparticles under investigation, Fe₃O₄ nanoparticles (NPs) are arguably the most extensively studied.^[15] Our group has paid much attention to nanoparticle-catalyzed organic reactions such as Hiyama cross-couplings, the amination of aryl iodides, the synthesis of propargylamines and tetrazoles, and so on.^[16] In continuation of our work on magnetic nanoparticles, we herein report the synthesis of o-hydroxybenzophenones under ligand-free conditions (Scheme 1). The experimental procedure is very simple, and the catalyst can be removed easily by an external magnet to be recycled.



Scheme 1. Synthesis of o-hydroxybenzophenones.

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Results and Discussion

The Fe₃O₄ nanoparticles were prepared according to a previously established procedure^[17] and were characterized by X-ray diffraction (XRD), transmission electron microscopy (TEM), and X-ray photoelectron spectroscopy (XPS). The acidity measurements of the Fe₃O₄ nanoparticles were performed by temperature-programmed desorption (TPD) of NH₃ and pyridine adsorption followed by FTIR spectroscopy. The XRD patterns of fresh and used Fe₃O₄ nanoparticles are shown in Figure 1.



Figure 1. XRD spectra of (a) fresh and (b) used Fe_3O_4 nanoparticles.

The XRD pattern recorded with $Cu-K_{\alpha}$ radiation shows characteristic peaks at $2\theta = 30.25$, 35.50, 43.38, 53.69, 57.23, and 62.77°, which correspond to (220), (311), (400), (422), (511), and (440) Bragg reflections, respectively. The XRD pattern agrees with standard magnetite (Fe_3O_4) (JCPDS: 65-3107), which identifies that the Fe₃O₄ nanoparticles adopt a cubic spinel structure.^[18] The size of the particles was calculated by the Debye-Scherrer formula on the basis of the full width at half-maximum of the high-intensity diffraction peak at $2\theta = 35.50^{\circ}$ and was found to be approximately 19 nm. This is in agreement with TEM analysis (Figure 2), which shows mainly spherical nanoparticles with a particle size in the range of 10–30 nm. Notably, the morphology and size of the particles were unaltered even after five cycles, which correlates well with the retention of catalytic activity after recycling. The selected-area electron diffraction (SAED) images also confirm the crys-



Figure 2. TEM and SAED images of Fe_3O_4 nanoparticles (a) before and (b) after use.

talline nature of both the fresh and used magnetic nanoparticles.

Elemental analysis and the relative composition of Fe³⁺ and Fe²⁺ were determined by using XPS. Fe₃O₄ is a mixedvalence compound with a conventional notation of [Fe³⁺]_{tet}-[Fe²⁺Fe³⁺]_{oct}O₄. It is of cubic inverse spinel crystal structure; the oxygen anions (O²⁻) form a closely packed facecentered cubic (fcc) sublattice in which the iron cations are located in the interstitial sites. There are two different kinds of cation sites: tetrahedrally coordinated sites occupied by Fe³⁺ and octahedrally coordinated sites occupied by Fe³⁺ and Fe²⁺ in equal numbers.^[18] The Fe²⁺cation can be considered to be Fe³⁺ plus an "extra" electron, and it undergoes rapid valence oscillation between the Fe^{III} and Fe^{II} octahedral sites. The survey scan of the Fe₃O₄ nanoparticles shows peaks characteristic of C1s (284.6 eV), O1s (529.9 eV), and Fe 2p (710 eV)^[19] (Figure 3). As can be seen in the inset of Figure 3, high-resolution narrow scans corresponding to Fe 2p of both the fresh and used catalyst could be deconvoluted into two peaks. The peaks centered at 710 and 723.6 eV correspond to Fe $2p_{3/2}$ and Fe $2p_{1/2}$, respectively, and are due to Fe in the +2 oxidation state.^[19] The peaks centered around 711.9 and 725.8 eV, corresponding to Fe $2p_{3/2}$ and Fe $2p_{1/2}$, respectively, are consistent with typical values for ferric oxides.[19]



Figure 3. XPS survey scans for (a) fresh and (b) used Fe_3O_4 nanoparticles [inset shows the high-resolution narrow scans for Fe 2p (a) fresh and (b) used Fe_3O_4 nanoparticles].

The total acidity of the Fe₃O₄ nanoparticles was measured by TPD of ammonia as well as pyridine adsorption followed by FT-TR spectroscopy. The desorption temperature and amount of ammonia desorbed are considered as indexes of acid strength and the total number of acid sites, respectively. A TPD peak at about 400 °C arises from desorption of ammonia from moderately strong acid sites (Figure S5, Supporting Information).^[19c] The FTIR spectrum of the pyridine adsorbed Fe₃O₄ nanoparticles shows a band at 1440 cm⁻¹, which is commonly assigned to Lewis acid sites. A trace amount of Brønsted acid sites is also present, which is indicated by the broad peak at 1560 cm⁻¹. However, the main contribution of acidity is due to Lewis acid sites (Figure S4, Supporting Information).^[19d]



Synthesis of *ortho*-Hydroxybenzophenones

The numerous advantages of iron make it highly attractive as a catalyst or reagent for chemical synthesis.^[20] The challenge of selective functionalization of phenols prompted us to investigate the reaction of phenol (**1a**) with 4-nitrobenzaldehyde (**2a**) in the presence of an iron catalyst (Table 1). It was found that Fe₃O₄ nanoparticles gave the best result as a catalyst in the reaction (Table 1, Entry 7), whereas anhydrous (anhy.) FeCl₃, Fe(acac)₃ (acac = acetylacetonate), Fe powder, and Fe₃O₄ showed low catalytic activity (Table 1, Entries 3–6). Fe(OAc)₂ and FeCl₃·6H₂O failed to give any oxidative coupling product (Table 1, Entries 1 and 2).

Table 1. Optimization of reaction conditions.[a]

OH N	$^{+}$ O_2N	_CHO _ca solv	talyst, base ▼ rent, air, 24 h	O ₂ N O	OH
1a Entry	2a	Solvent	Pasa	Ja	Viald
Enuy	Catalyst	Solvent	Dase	[°C]	[%] ^[b]
1	Fe(OAc) ₂	toluene	K ₂ CO ₃	110	-
2	FeCl ₃ •6H ₂ O	toluene	K ₂ CO ₃	110	_
3	anhy. FeCl ₃	toluene	K ₂ CO ₃	110	25
4	Fe(acac) ₃	toluene	K ₂ CO ₃	110	16
5	Fe powder	toluene	K ₂ CO ₃	110	19
6	Fe ₃ O ₄	toluene	K ₂ CO ₃	110	9
7	Fe ₃ O ₄ NPs	toluene	K ₂ CO ₃	110	55, 0 ^[c,d]
8	Fe ₃ O ₄ NPs	CH ₃ CN	K ₂ CO ₃	80	trace
9	Fe ₃ O ₄ NPs	water	K ₂ CO ₃	100	_
10	Fe ₃ O ₄ NPs	EtOH	K ₂ CO ₃	78	trace
11	Fe ₃ O ₄ NPs	DMF	K ₂ CO ₃	152	trace
12	Fe ₃ O ₄ NPs	toluene	Cs_2CO_3	110	30
13	Fe ₃ O ₄ NPs	toluene	Et ₃ N	110	_
14	Fe ₃ O ₄ NPs	toluene	K ₂ CO ₃	25	trace
15	Fe ₃ O ₄ NPs	toluene	Na ₂ CO ₃	110	35
16	Fe ₃ O ₄ NPs	toluene	NaOH	110	trace
17	Fe ₃ O ₄ NPs	toluene	KtOBu	110	trace
	otion conditio	no: 10 (1.3 mmol)	2a (1 mmol)	cotolyst

[a] Reaction conditions: **1a** (1.3 mmol), **2a** (1 mmol), catalyst (20 mol-%), base (2.2 mmol), solvent (3 mL). [b] Isolated yield. [c] In the absence of a catalyst. [d] In the absence of base.

Later, we optimized the reaction conditions further by screening different solvents, bases, and temperatures. Finally, the optimal conditions were obtained, that is, catalyst (20 mol-%), **1a** (1.3 equiv.), **2a** (1 equiv.), K_2CO_3 (2.2 equiv.), toluene (3 mL), and the reaction was performed at 110 °C for 24 h.

Under these optimized conditions, the reaction scope was explored with various arenecarbaldehydes and phenols (Table 2). Arenecarbaldehydes with electron-withdrawing and electron-donating substituents gave the desired products in almost similar yields when treated with the same phenol [40–64% (Table 2, Entries 1–7) vs. 50–67% (Table 2, Entries 8 and 9)]. However, the results showed that substituents on the phenol played an important role, which is in contrast to what was observed for substituted arenecarbal-

dehydes. Phenol substituted with an electron-donating *tert*butyl group (i.e., **2b**) offered a higher yield than unsubstituted phenol (i.e., **2a**); conversely with electron-deficient 4nitrophenol (**2c**), no reaction was detected with aldehydes containing either an electron-withdrawing group (Table 2, Entry 10) or an electron-donating group (Table 2, Entry 11). This is not unexpected, as electron-donating substituents in the *para* position of phenol decrease the bond dissociation energies (BDEs) of the O–H bonds of substituted phenols by raising the ground-state energies. Alternatively, electron-withdrawing substituents in the *para* position interact with the O–H dipoles and cause a lowering of the ground-state energies, which thereby increases the BDE(O–H) values.^[21]

Table 2. ortho-Benzoylation of phenols with aryl aldehydes.[a]

F	CHO + 1a–g	OH R ² 2a-c	Fe ₃ 0	D ₄ , K ₂ CO ₃ ne, 110 °C ir, 24 h	►	O OH R ² 3
Entry		\mathbb{R}^1		R ²	Product	Yield [%] ^[b]
1	1a	4-NO ₂	2a	Н	3 aa	55
2	1b	4-Cl	2a	Н	3ba	64
3	1c	4-Br	2a	Н	3ca	52
4	1d	4-CF ₃	2a	Н	3da	45
5	1e	4-CN	2a	Н	3ea	40
6	1f	4-CH ₃	2a	Н	3fa	60
7	1g	3-NO ₂	2a	Н	3ga	50
8	1 a	4-NO ₂	2b	<i>t</i> Bu	3ab	67
9	1b	4-Cl	2b	<i>t</i> Bu	3bb	50
10	1a	4-NO ₂	2c	NO ₂	3ac	-
11	1f	4-CH ₃	2c	NO_2	3fc	_

[a] Reaction conditions: Fe_3O_4 (20 mol-%), aldehyde (1 mmol), phenol (1.3 mmol), K_2CO_3 (2.2 mmol), toluene (3 mL), 110 °C, air, 24 h. [b] Isolated yield.

When 2-substituted arenecarbaldehydes were treated with phenols, xanthones were obtained in good yields in one step (Table 3). Xanthones constitute the core of many natural products and biologically active compounds. They exhibit diverse physicochemical and pharmacological properties, including antitumoral, antibacterial, and anti-inflammatory activities.^[22] 2-Nitrobenzaldehyde (**1h**) produced the corresponding xanthone in good yields (Table 3, Entries 1 and 4), but 2-chloro- and 2-bromobenzaldehydes gave lower yields, which is likely due to a cross-coupling reaction between the halogen and the hydroxy groups (Table 3, Entries 2 and 3). It is believed that, first, the 2-substituted aldehyde reacts with phenol to give the corresponding *ortho*-benzoylation product and, second, under basic conditions, the *ortho*-substituent of the aldehydes serves as a leaving

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group, which leads to the final product. Unfortunately, the present method is not amenable to aliphatic aldehydes.

Table 3. One-step synthesis of xanthones.^[a]

	CHO R ¹	+ R ²	Fe ₃ O toluer	^{4,} K ₂ CO ₃ ne, 110 °C ir, 24 h		R ²
Entry		\mathbb{R}^1		R ²	Product	Yield [%] ^[b]
1	1h	2-NO ₂	2a	Н	4a	65
2	1i	2-C1	2a	Н	4a	55
3	1j	2-Br	2a	Н	4a	50
4	1h	2-NO ₂	2b	tBu	4b	72
5	1h	2-Br	2b	tBu	4b	55
6	1h	2-NO ₂	2c	H[c]	4c	60

[a] Reaction conditions: Fe₃O₄ (20 mol-%), aldehyde (1 mmol), phenol (1.3 mmol), K₂CO₃ (2.2 mmol), toluene (3 mL), 110 °C, air, 24 h. [b] Isolated yield. [c] 1-Naphthol.

To check the recyclability of the catalyst, as can be seen from Table 4, the reaction was performed with 4-nitrobenzaldehyde and phenol under the optimized reaction conditions. After completion of the reaction, the catalyst was easily separated from the reaction mixture with an external magnet and could be reused in the next cycle. The Fe_3O_4 nanoparticles were used over five runs, and no obvious loss in the catalytic activity was observed. This indicated that the Fe_3O_4 nanoparticle catalyst had great recyclability in this reaction.

Table 4. Recycling of the catalyst.^[a]

Run	Yield [%] ^[b]	Run	Yield [%] ^[b]
1	55	4	50
2	52	5	48
3	51		

[a] Reaction conditions: 4-nitrobenzaldehyde (1 mmol), phenol (1.3 mmol), Fe₃O₄ (20 mol-%), K_2CO_3 (2.2 mmol), toluene (3 mL). [b] Isolated yield.

Regarding the mechanism, it is generally believed that this reaction is a Friedel–Crafts-type reaction that involves the nucleophilic addition of phenols to aldehydes under basic conditions, and this is then followed by dehydrogenative oxidation in air to give the *ortho*-benzoylation products.^[14,23] During this process, the Fe₃O₄ nanoparticles act as a Lewis acid to activate the carbonyl group and stabilize the reactive intermediates. The presence of Lewis acidic sites on the surface of Fe₃O₄ nanoparticles is confirmed from FTIR and TPD of NH₃ studies. A plausible mechanism is shown in Scheme 2. However, for aldehydes having good leaving groups as *ortho* substituents, ring-closed xanthones will form automatically.



Scheme 2. A plausible mechanism.

Conclusions

We have developed a simple method for the synthesis of 2-hydroxybenzophenones through *ortho*-benzoylation by using magnetically retrievable Fe_3O_4 nanoparticles as the catalyst under ligand-free conditions. This method is also useful for the preparation of xanthones in good yields. The simple procedure for the preparation of the catalyst and its easy recovery and reusability are expected to contribute to its utilization in the development of benign chemical processes and products.

Experimental Section

Preparation of Fe₃O₄ Nanoparticles:^[17] FeSO₄·7H₂O (13.9 g) and Fe₂(SO₄)₃ (20 g) were dissolved in H₂O (500 mL) in a 1000 mL beaker. NH₄OH (aq., 25%) was added slowly to adjust the acidity of the solution to pH = 10. The reaction mixture was then continually stirred at 60 °C for 1 h. The precipitated nanoparticles were separated magnetically, washed with water until pH = 7, and then dried under vacuum at 60 °C for 2 h.

General Procedure for *ortho*-Benzoylation of Phenols with Arenecarbaldehydes: Phenol (1.3 equiv.), arenecarbaldehyde (1 equiv.), K_2CO_3 (2.2 equiv.), and the Fe₃O₄ nanoparticles (20 mol-%) were added to toluene (3 mL), and the reaction mixture was stirred at 110 °C for 24 h. Upon completion of the reaction, the catalyst was easily separated from the reaction mixture with an external magnet. Then, the reaction mixture was extracted with dichloromethane (3 × 10 mL) and washed with brine, and the combined organic layers were dried with anhydrous Na₂SO₄. The organic phase was concentrated under vacuum, and the residue was purified by flash column chromatography on silica gel to afford the pure product.

Supporting Information (see footnote on the first page of this article): Experimental procedures, data for the *ortho*-benzoylation products and the xanthones, and ¹H and ¹³C NMR spectra for all compounds.

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Synthesis of ortho-Hydroxybenzophenones

The applicability of magnetically retriev-

able Fe_3O_4 nanoparticles in the oxidative

coupling of aryl aldehydes with phenols

under ligand free conditions is demon-



T. Ramani,* P. Umadevi, K. L. Prasanth,* B. Sreedhar* 1–7

Synthesis of *ortho*-Hydroxybenzophenones Catalyzed by Magnetically Retrievable Fe₃O₄ Nanoparticles under Ligand-Free Conditions

Keywords: Iron / Nanoparticles / Benzoylation / Lewis acids / Heterogeneous catalysis

Oxidative Coupling

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