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One-Step Synthesis of Xanthones Catalyzed by a Highly Efficient Copper-Based Magnetically Recoverable Nanocatalyst

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S *Supporting Information*

ABSTRACT: A versatile and highly efficient strategy to construct a xanthone skeleton via a ligand-free intermolecular catalytic coupling of 2-substituted benzaldehydes and a wide range of phenols has been developed. For this purpose, a novel and magnetically recoverable catalyst consisting of copper nanoparticles on nanosized silica coated maghemite is presented. The reaction proceeds smoothly with easy recovery and reuse of the catalyst. The methodology is compatible with various functional groups and provides an attractive protocol for the generation of a small library of xanthones in very good yield.

Xanthones (9*H*-xanthen-9-ones) are a special class of oxygenated heterocyclic compounds with important biological activities.[1] This family of compounds are structurally typified by the presence of a dibenzo-γ-pirone system differing in the position and nature of the substituents. This molecular diversity provides a wide variety of pharmacological properties; e.g.. the xanthone skeleton constitutes the core of an important group of natural and biologically active compounds such as bikaverin,[2] psorospemin,[3] and α-mangostin[4] (Figure 1). Moreover, the biological behavior of xanthones can be controlled by introducing specific substituents in their structure.[5]

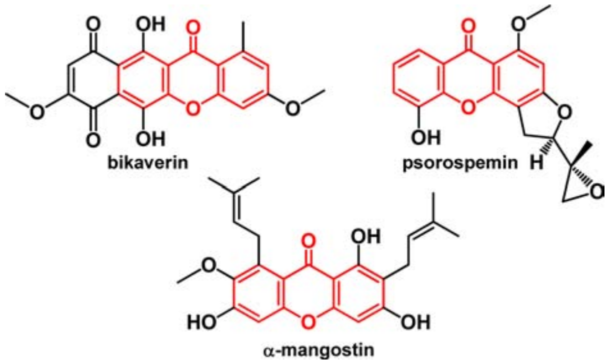

Figure 1. Some representative natural xanthones.

Considering that in xanthones derived from natural sources the type and position of substituents are imposed by biosynthetic pathways, the organic synthesis emerges as an essential tool for the construction and design of new functionalized xanthonic skeletons.

In this sense, most of the traditional methods to access the synthesis of xanthones involve several steps.[6] Therefore, the search for a synthetic protocol that is operationally desirable requiring fewer reaction steps currently represents an enormous challenge for the synthetic organic chemists. In recent years, a number of attractive synthetic approaches to xanthones have been developed,[7] generally involving the use of diaryl ethers or benzophenone derivatives as starting materials. Among them, very recently, Li and co-workers reported a novel strategy to synthesize a xanthone skeleton via an intramolecular rhodium-catalyzed cross-dehydrogenative coupling (CDC) of 2-aryloxybenzaldehydes.[8]

One-step synthesis of xanthones from easily accessible starting materials is extremely rare. Recently, Wang and co-workers[9] established an intermolecular catalytic *ortho*-acylation of phenols with various aryl aldehydes using $CuCl_2$ as the catalyst in the presence of triphenylphosphine. This methodology allowed the synthesis of xanthones in one step and in high yield; however, the need to employ activated phenols (substituted with electron-donating groups), phosphine ligands, and long reaction times (24 to 48 h) represents the main drawbacks of this protocol.

On the other hand, the development of efficient and selective copper-based catalysts has increased significantly in recent years, mainly due to not only economic and environmental considerations but also the low toxicity of copper compared with other transition metals, which is essential from the green chemistry perspective. In this context, the synthesis of transition metal nanoparticles and their application in catalysis have received considerable attention in recent years.[10]

In recent years, some of us have been actively working on new methodologies for the preparation of copper nanoparticles (CuNPs) and their application in important organic transformations.[11] These methodologies are simple and economic

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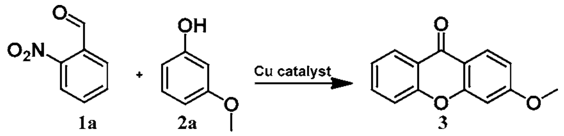
ones and include the fast reduction of copper(II) chloride with lithium sand and a catalytic amount of an arene as the electron carrier, under mild reaction conditions. More recently, the same methodology was applied for the synthesis of CuNPs supported on silica coated maghemite (MagSilica), which proved to be a versatile, magnetically recoverable, and reusable catalyst for various alkyne coupling and cycloaddition reactions.[12]

Inspired by the work by Wang and co-workers,[9] and with the aim to develop an operationally simple synthesis of the xanthone core, we decided to study the course of the acylation reaction between *ortho*-substituted benzaldehydes and phenols, catalyzed by our magnetic nanocatalyst consisting of CuNPs on silica coated maghemite.

The reaction conditions for the copper-catalyzed intermolecular *O*-acylation reaction were optimized by using 2-nitrobenzaldehyde (**1a**) and 3-methoxyphenol (**2a**) as model substrates.

In a first series of experiments we evaluated the catalytic activity of six different copper-based catalysts on the reaction outcome (Table 1), working under standard conditions (toluene, K_3PO_4, PPh_3, 110 °C, 24 h).

Table 1. Initial Screening of Some Copper Catalysts[a]



entry	catalyst	yield (%)[b]
1	$CuCl_2 \cdot H_2O$	–
2	$CuCl_2$	75
3	Cu	71
4	CuCl	65
5	CuNPs/MagSilica	89
6	CuO	62
7	***CuNPs/MagSilica***	***88***[c]

[a] Standard reaction conditions: 2-nitrobenzaldehyde (1 mmol), 3-methoxyphenol (1.3 mmol), Cu catalyst (5 mol %), PPh_3 (7.5 mmol), K_3PO_4 (2.2 equiv) in toluene, 24 h. [b] Determined by GC using internal standard. [c] Reaction performed using only 0.9 mol % (8 mg) of CuNPs/MagSilica catalyst.

The possibility of using different copper sources to perform the target cyclization, regardless of their oxidation state, makes this methodology advantageous and attractive from a synthetic point of view. Thus, the use of different commercially available copper sources (Cu, $CuCl_2$, CuCl, CuO) led to xanthone **3** in good yields.

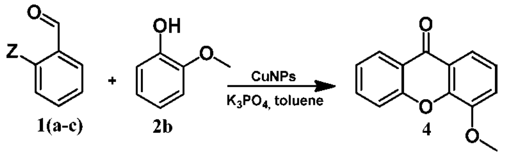
To our great satisfaction, we found that our CuNPs magnetic nanocatalyst was the most efficient for the desired transformation. Furthermore, as will be commented below, the catalyst can be easily recycled by means of an external magnet and reused without significant loss of catalytic activity.

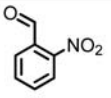
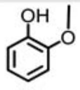
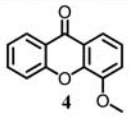
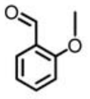
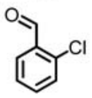
Then, we optimized the catalyst loading. As shown in Table 1, we started our study by using 5 mol % of copper (45 mg of CuNPs catalyst) thus obtaining the desired xanthone product in 89% yield. We were delighted to find that the reaction proceeded with the same efficiency and selectivity by using a catalyst loading as low as 0.9 mol % of copper (8 mg of CuNPs catalyst).

We next carried out a systematic screening of solvents, ligands, temperatures, and bases (see Supporting Information for experimental details). These combined studies demonstrated that the optimal conditions for the one-step synthesis of the desired xanthone included using toluene as the solvent at 110 °C, K_3PO_4 as the base (2.2 equiv referred to the starting benzaldehyde), 8 mg (0.9 mol % copper) of the CuNPs catalyst, 1 mmol of aryl aldehyde, and 1.1 mmol of phenol for 2 h. Remarkably, we discovered that the presence of a phosphine ligand is not necessary for the success of the reaction.

Then, the scope of the method, with respect to the leaving group, was evaluated by reacting different 2-substituted benzaldehydes with 2-methoxyphenol (**2b**) under the optimized conditions (Table 2).

Table 2. Scope of 2-Substituted Benzaldehydes[a]



entry	aryl aldehyde	phenol	xanthone	yield (%)[b]
1	 **1a**	 **2b**	 **4**	84
2	 **1b**	2b	4	65
3	 **1c**	2b	4	61

[a] Reaction conditions: aryl aldehyde (1 mmol), 2-methoxy-phenol (1.1 mmol), CuNPs (0.9 mol %), K_3PO_4 (2.2 equiv), 2 h, under argon. [b] Isolated yield after purification.

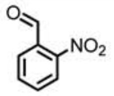
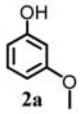
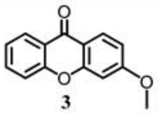
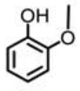
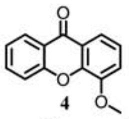
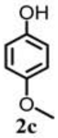
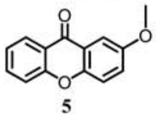
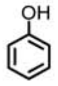
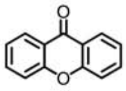
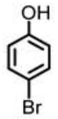
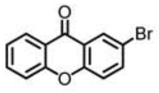
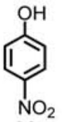
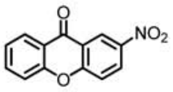
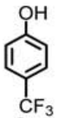
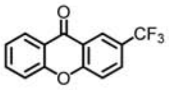
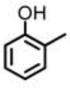
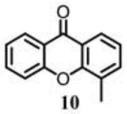
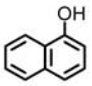
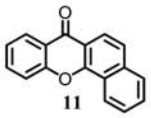
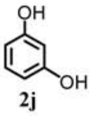
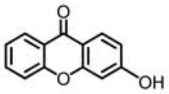
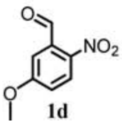
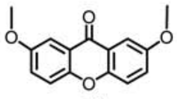
As shown in Table 2, 2-nitro-, 2-methoxy-, and 2-chlorobenzaldehyde (**1a**, **1b** and **1c**, respectively) produced the corresponding xanthones in good yields (61–84%).

Since the nitro group gave better results than the other leaving groups tested, the scope and the general efficiency of the method was then analyzed by studying the reaction of 2-nitrobenzaldehydes with a wide range of phenols under the optimized conditions (Table 3).

The results shown in Table 3 indicate that the synthetic protocol is compatible with the presence of a variety of functional groups in the starting phenols, including the nitro, bromo, methoxy, alkyl, trifluoromethyl, and free phenolic hydroxyl group, affording the desired xanthones in good to excellent yields.

With regard to the electronic properties of the substituents, the presence of electron-donating groups on the aromatic ring of the starting phenols led to better yields of the cyclization products (entries 1, 2, 3, and 8). It should be noted that using our CuNPs-based magnetic catalyst allowed the synthesis of xanthones starting from phenols bearing electron-withdrawing groups (entries 6 and 7), thus overcoming one of the limitations reported by Wang's group. However, when a strong electron-withdrawing group was introduced, the isolated yield

Table 3. Synthesis of Xanthones from 2-Nitrobenzaldehydes with Phenols[a]

entry	aryl aldehyde	phenol	xanthone	yield (%)[b,c]
1	 **1a**	 **2a**	 **3**	97 (86)
2	1a	 **2b**	 **4**	91 (84)
3	1a	 **2c**	 **5**	98 (89)
4	1a	 **2d**	 **6**	84 (76)
5	1a	 **2e**	 **7**	78 (70)
6	1a	 **2f**	 **8**	60 (51)
7	1a	 **2g**	 **9**	63 (54)
8	1a	 **2h**	 **10**	89 (80)
9	1a	 **2i**	 **11**	85 (77)
10	1a	 **2j**	 **12**	75 (68)
11	 **1d**	**2c**	 **13**	85 (72)

[a] Reaction conditions: aryl aldehyde (1 mmol), phenols (1.1 mmol), CuNPs (0.9 mol %), K_3PO_4 (2.2 equiv), 2 h, under argon. [b] Determined by GC using internal standard. [c] Isolated yield.

dropped to 51% (entry 6). Finally, we selected the one-step synthesis of xanthone **3** as the model reaction for the study of the catalyst performance after various cycles of recovery and reuse. It is worthy of note that, despite the small amount of catalyst utilized (8 mg), it could be separated from the reaction medium, washed (ethyl acetate), dried under vacuum, and reused, simply with the aid of a permanent magnet placed on the outer wall of the reaction flask, thus minimizing the loss of catalyst which usually occurs in filtration processes. Figure 2 shows the catalyst performance for the coupling of 2-nitrobenzaldehyde (**1a**) with 3-methoxyphenol (**2a**) under the optimized conditions, after four consecutive cycles without significant loss of catalytic activity.

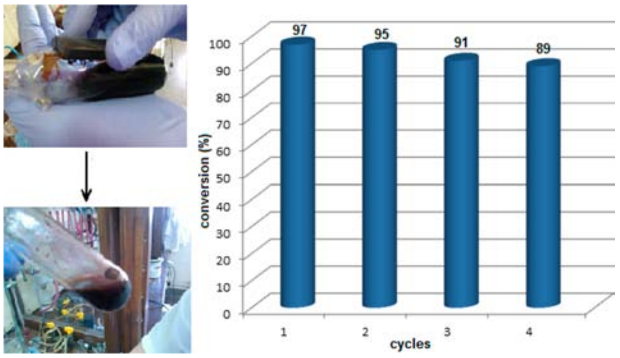


Figure 2. Recovery and recycling of the catalyst in the one-step synthesis of xanthone **3**.

The low diminution in the activity from the first to the fourth cycle may be related to small losses of catalyst mass during the washing procedure. It is important to note that the total mass of catalyst employed is very low (8 mg); thus, the loss of only 1 mg of catalyst when handling the sample means a loss of 12.5% of the total mass of catalyst.

Although the detailed reaction mechanism is not definite at this stage, as proposed by Wang et al.[9] we think that the cyclization reaction could take place thorugh a Friedel–Crafts type process, via a nucleophilic addition of phenol **2** to the *ortho*-substituted benzaldehyde **1** under basic conditions, followed by a dehydrogenative oxidation to give the *ortho*-acylated intermediate **A** (Figure 3).

The formation of intermediate **B** through an acid–base coordination between CuNPs and the phenolic oxygen could evolve into an intermediate of the type **C** in which CuNPs are coordinated with the phenolic oxygen and the leaving group,

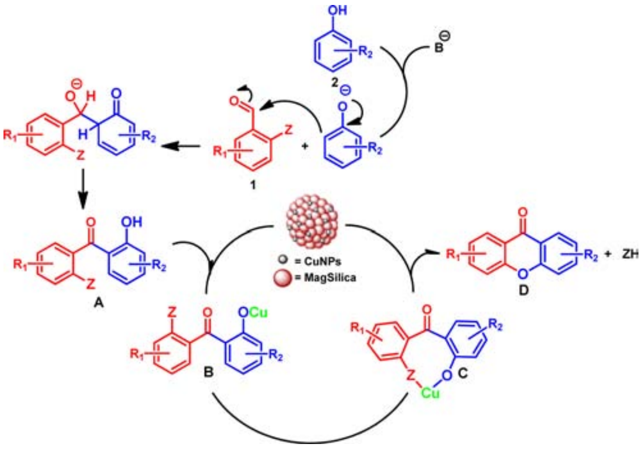


Figure 3. Plausible reaction mechanism for the CuNPs-catalyzed one-step synthesis of xanthones.

leading to the xanthone **D** through an intramolecular aromatic nucleophilic substitution, favored by the presence of an electron-withdrawing group at the *ortho* position.

In summary, a magnetically recoverable copper-based catalyst composed of CuNPs (ca. 3.0 nm) on nanosized silica coated maghemite proved to be a highly efficient heterogeneous catalyst for the one-step ligand-free synthesis of functionalized xanthones. Of note are the drastic reduction in reaction times (from 24 to 2 h) and the higher functional group tolerance observed when compared to other recently reported copper-based protocols.

The catalyst could be easily recycled by means of an external magnet and reused four times without significant loss of catalytic activity. The easy recovery of the catalyst, together with the negligible leaching of metal species (<50 ppb of copper were detected by ICP-AES) and the high atom economy involved in the transformations studied, make this methodology especially attractive from a green chemistry perspective. Although the experimental observations led us to suggest a heterogeneous catalytic process, it should not be discarded that the copper supported nanocatalyst could be acting as a reservoir for metal species that leach into solution and readsorb.[13]

The potential scalability of the process and the simple reaction conditions, combined with the low cost of the starting materials, make this new protocol transferable to pharmaceutical purposes. Efforts to extend this protocol to nontraditional methodologies such as the use of microwave irradiation and further mechanistic studies are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of all xanthones prepared. Full characterization of catalyst is also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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