One-pot synthesis of xanthones using a novel copper-based magnetically recoverable nanocatalyst

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Abstract

A versatile and straightforward strategy to construct a xanthone skeleton *via* an 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 in absence of ligand is presented. The reaction proceeds smoothly without the need to preactivate the aldehyde carbonyl group. It can tolerate various functional groups and provides an efficient protocol for the generation of a small library of xanthones in high yield.

Keywords: xanthones, copper nanoparticles, synthesis, intermolecular coupling, magnetic nanocatalyst.

Introduction

Natural product synthesis is a highly demanding field in constant need of efficient transformations that allow either straightforward, scalable, and high-yielding preparation of starting materials or especially tolerant reactions that can be used in end game strategies on complex substrates to install a certain functional group with the utmost delicacy and surgical precision.

Xanthones (9*H*-xanthen-9-ones) are naturally occurring bioactive heterocyclic compounds with the dibenzo-γ-pyrone framework. The xanthone skeleton constitutes the core of an important family of natural and biologically active compounds that are widespread in higher plants and microorganisms. These secondary metabolites have interesting pharmaceutical properties, among them anti-cancer, anti-thrombotic, anti-hypertensive, anti-bacterial, anti-tumoral, opiaceous, cytotoxic, anti-viral and anti-inflammatory activity [1]. The xanthone scaffold has even been described as "privileged structure", since members of this structural class are able to interact with different types of drug targets and attracted interests across a broad spectrum of sciences from chemistry and biology to medicine The biological role of xanthones can be modulated by introducing specific substituents in their structure (Figure 1) [2].
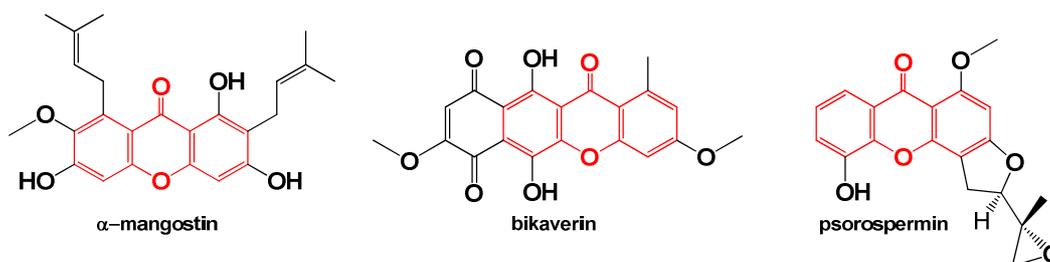
Figure 1. Relevant natural xanthones.

Due to the unique chemical structures and good pharmacological activities, many efforts have been done by different research groups aimed to synthesize xanthone derivatives as novel drug candidates. Standard syntheses of the xanthone skeleton typically involve multistep procedures, which generally require the intermediacy of a benzophenone or a diaryl ether, plus harsh reaction conditions, and/or strong acids or toxic metals are often employed [3]. Therefore, the search for an operationally convenient, modular, and broadly applicable xanthone synthesis still represents a challenging research task.

On the other hand, the interest in the development of efficient and selective copper-based catalysts has increased continuously in recent years, mainly because of economical and environmental considerations but also due to 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 [4]. Due to their high surface area, these nanosized metal particles often show unique catalytic properties, and are considered to be on the frontier between the homogeneous and heterogeneous catalysis, preserving the main advantages of both methodologies, i.e. high activity (and selectivity) and easy recyclability. However, in practice, the separation and recovery of these nanocatalysts from the reaction medium by using standard techniques (filtration, centrifugation) is not always easy due to the nanometric size of the particles. To overcome this drawback, metal nanoparticles are supported over a variety of organic and inorganic supports. Among them, magnetic nanomaterials have emerged lately as a very attractive alternative since their high surface area allows higher catalyst loading than many conventional supports, and their magnetic properties enables the simple and efficient recovery of the catalyst by means of an external magnet [5].

In the last 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. These methodologies are simple and economic ones, and consist in the fast reduction of copper (II) chloride with lithium sand and a catalytic amount of an arene as electron carrier, under mild reaction conditions. We have found that by using this methodology, $CuCl_2$ or $CuCl_2.2H_2O$ are suitable precursors for the synthesis of very reactive CuNPs, with a size distribution in the range of 3.0±1.5 nm [6]. These CuNPs, both naked [7] or dispersed on inorganic supports [8], efficiently promoted important

synthetic transformations. More recently, the same methodology was applied for the synthesis of CuNPs supported on silica coated maghemita (MagSilica®), which showed to be a versatile, magnetically recoverable and reusable catalyst for various alkyne coupling and cycloaddition reactions [9]. In this context, and considering the experience of our group in the preparation of heterocycles through copper-assisted coupling processes, herein, we establish an efficient synthetic method to access the xanthone substructure *via* an intermolecular catalytic coupling from 2-substituted benzaldehydes and phenols in the presence of a novel copper-based magnetically recoverable nanocatalyst. Taking into account the easy setup, recyclability and the sustainability of this procedure, it could be transferred to industrial purposes.

Experimental section

Materials

All moisture sensitive reactions were carried out under an argon atmosphere. Solvents were dried and distilled in accordance with standard procedure [10]. Reactions were monitored by thin-layer chromatography on silica gel plates (60F-254) visualized under UV light and/or using 5% phosphomolybdic acid in ethanol. Column chromatography was performed over silica gel 60 (70-230 mesh). All starting materials were of the best available grade (Aldrich, Merck) and were used without further purification. Commercially available copper (II) chloride dihydrate was dehydrated upon heating in oven (150 °C, 45 min) prior to use for the preparation of CuNPs. MagSilica® was provided by Evonik Industries AG (Essen, Germany).

CuNPs/MagSilica catalyst preparation

A mixture of lithium sand (21 mg, 3.0 mmol) and 4,4'-di-*tert*-butylbiphenyl (DTBB, 26 mg, 0.1 mmol) in THF (3 mL), was stirred at room temperature under nitrogen atmosphere. When the reaction mixture turned dark green (15-30 min), indicating the formation of the corresponding lithium arenide, anhydrous $CuCl_2$ was added (134 mg, 1.0 mmol). The resulting suspension was stirred until it turned black (15-30 min), indicating the formation of copper(0) nanoparticles. Then, it was diluted with THF (10 mL) and MagSilica (500 mg) was added. The resulting suspension was stirred for 1 h, and then bidistilled water (2 mL) was added for eliminating the excess of lithium. The resulting solid was filtered under vacuum in a Buchner funnel and successively washed with water (10 mL) and acetone (10 mL). Finally, the solid was dried under vacuum (5 Torr) for 2 h.

Instrumentation and analysis

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 spectrophotometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. Mass spectra (EI) were obtained at 70 eV on a Hewlett Packard HP-5890 GC/MS instrument equipped with a HP-5972

selective mass detector. The purity of volatile compounds and the chromatographic analyses (GC) were determined with a GC Shimadzu (GC-14B) with a flame ionization detector equipped with a HP-5MS column (30 m × 0.25 mm × 0.25 µm) using nitrogen as carrier gas.

The CuNPs/MagSilica catalyst was characterized by means of transmission electron microscopy (TEM), energy dispersive X-ray (EDX), powder X-ray diffraction (XRD), temperature programmed reduction (TPR), and inductively coupled plasma atomic emission spectroscopy (ICP-AES). Detailed results of catalyst characterization were reported elsewhere [9].

Xanthones described were characterized by comparison of their ^{1}H, and/or ^{13}C NMR and IR spectra to the previously reported data [11].

General Procedure for One-step Synthesis of Xanthones

Phenols (1.3 mmol), 2-substituted benzaldehydes (1 mmol), K_3PO_4 (2.2 equiv.), CuNPs (5 mol%), and toluene (3 mL) were added to a Schlenk tube under air. The resulting solution was stirred at 110 °C for 2 h. The mixture was extracted with EtOAc, washed with water, brine, and then the combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel to afford the products.

Results and Discussion

One-step synthesis of xanthones from relatively simple starting materials is extremely rare. Recently, Wang and co-workers [11] developed an intermolecular catalytic *ortho*-acylation of phenols with various aryl aldehydes in-depth using $CuCl_2$ as the catalyst in the presence of triphenylphosphine. Furthermore, this method can be used to synthesize xanthones in one step and in high yield. The main drawbacks of this protocol involve the need to employ activated phenols (presence of electron-donating groups) and high reaction times (24 to 48 h). Inspired by these results and with the aim to develop a simple operational synthesis method of xanthone core, we decided to study the course of the copper-catalyzed acylation reaction between *ortho*-substituted benzaldehydes and phenols.

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 tested 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). The possibility of using different copper sources, regardless of their oxidation state, to perform the target cyclisation 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, $CuCl_2.2H_2O$) led to xanthone **3aa** in good yields.

Table 1: Initial screening of some copper-catalysts[a]
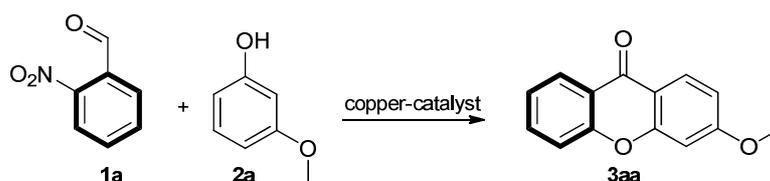
Entry	catalyst	Yield (%)[b]
1	$CuCl_2 \cdot 2H_2O$	---
2	$CuCl_2$	75
3	$Cu°$	71
4	CuCl	65
5	**CuNPs**	**89**
6	CuO	62

[a] **Standard reaction conditions:** 2-nitro-benzaldehyde (1 mmol), 3-methoxyphenol (1.3 mmol), [Cu] (5 mol %), PPh_3 (7.5 mmol), K_3PO_4 (2.2 eq.) in toluene), 24 h. [b] Determined by GC using internal standard.

To our satisfaction, we found that the copper-nanocatalyst prepared recently by our group [6] demonstrated to be 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.

Employing this novel catalyst consisting of copper nanoparticles on nanosized silica coated maghemite, we next investigated the influence of the solvent and of the addition of a ligand on the course of the reaction (Table 2). Using 5 mol% of catalyst, we discovered that the presence of phosphine ligand is not crucial to the success of the reaction. On other hand, the screening of the reaction solvent demonstrated that toluene was superior to others such as DMF, DMSO, and protic solvent H_2O.

Table 2: Effect of ligand and solvent on copper-mediated coupling reaction[a]

Entry	ligand	solvent	Yield (%)[b]
1	PPh_3	toluene	89
2	---	**toluene**	**95**
3	PPh_3	H_2O	---
4	---	H_2O	---
5	PPh_3	DMF	64
6	---	DMF	62
7	PPh_3	DMSO	51
8	---	DMSO	51

[a] **Reaction conditions:** 2-nitrobenzaldehyde (1 mmol), 3-methoxyphenol (1.3 mmol),CuNPs (5 mol %), PPh_3 (7.5 mmol), K_3PO_4 (2.2 eq.), 24 h. [b] Determined by GC using internal standard.

Finally, we optimized the reaction temperature. As shown in Table 3, when we operate at both low temperature and at room temperature the reaction did not proceed. On the contrary, when heated at 110 ° C, the reaction was surprisingly complete in only 2 h of reaction time and in high yield.

Table 3. Temperature effect on copper-catalyzed reaction[a]

Entry	T (°C)	t (h)	Yield (%)[b]
1	0	48	---
2	RT	48	---
3	70	24	53
4	**110**	**2**	**95**

[a] *Reaction conditions*: 2-nitrobenzaldehyde (1 mmol), 3-methoxyphenol (1.3 mmol),CuNPs (5 mol %), K_3PO_4 (2.2 eq.). [b] Isolated yield after purification.

Then, the scope of this methodology was evaluated by reacting different 2-substituted benzaldehydes with 2-methoxyphenol (**2b**) under the optimized conditions.

Table 4. One-step synthesis of xanthones from 2-methoxyphenol (**2b**) with 2-substituted benzaldehydes[a]

Entry	aryl aldehyde	phenol	xanthone	Yield[b]
1	**1a**	**2b**	**3ab**	84 %
2	**1b**	**2b**	**3bb**	65 %
3	**1c**	**2b**	**3cb**	61 %

[a] *Reaction conditions*: 2-substituted benzaldehyde (1 mmol), 2-methoxyphenol (1.3 mmol),CuNPs (5 mol %), K_3PO_4 (2.2 eq.), 2 h, under air. [b] Isolated yield after purificaton.

As shown in Table 4, 2-nitro-, 2-methoxy- and 2-chlorobenzaldehyde (**1a**, **1b** and **1c**, respectively) produced the corresponding xanthones in good yields (63–87%). It is believed that the ring-closed xanthone products are achieved *via ortho*-acylation of phenols with 2-substituted aryl aldehydes first,

and then, under basic conditions, the *ortho*-substituents of aldehydes serving as leaving groups lead to the final ring-closed xanthones. Since the nitro group gave better results than other leaving groups, the scope and the general efficiency of the method was then demonstrated by reaction of 2-nitrobenzaldehyde with a wide range of phenols under the optimized conditions (Table 5).

The results shown in Table 5 indicate that the protocol is compatible with a variety of functional groups in the starting phenols, including nitro, bromo, methoxy, alkyl and a free phenolic OH function. The presence of electron-donating groups on the aromatic ring of phenols led to better yields of the cyclization products (entries 1, 2,3 and 7). It should be noted, that using our CuNPs-based magnetic catalyst allowed the synthesis of xanthones starting from phenols bearing electron-withdrawing groups (entry 6), thus overcoming the limitations reported by the group of Wang [11].

Finally, we selected the one-step synthesis of xanthone (**3aa**) as model reaction for the study of the catalyst performance after various cycles of recovery and reuse. It is worthy of note that, even though the small amount of catalyst utilized (8 mg), it could be separated from the reaction medium, washed and reused very easily, 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 with 3-methoxyphenol in the presence of toluene, after four consecutive cycles without significant loss of catalytic activity. The low diminution in the activity from the first to the fourth cycle would be related with small losses of catalyst mass during 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 loss of 12 % of the total mass of catalyst.
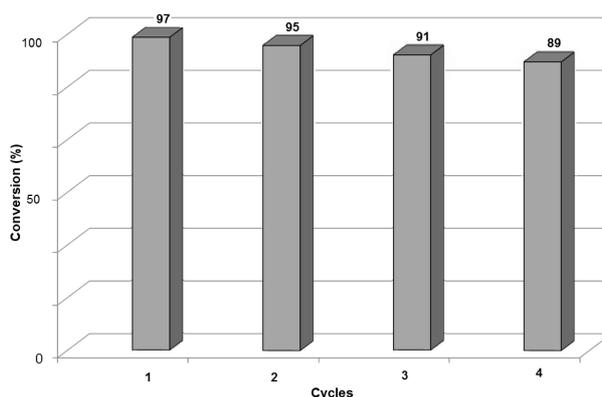
Figure 2. Catalyst performance in the one-step synthesis of xanthones.

Although the detailed reaction mechanism is not very definitive, it is conceivable that this is a Friedel–Crafts type reaction, which involves the nucleophilic addition of phenols to aldehydes under basic conditions, followed by a dehydrogenative oxidation in air to give *ortho*-acylation products [12]. If *ortho*-substituents of aldehydes are good leaving groups, ring-closed xanthones will form

automatically. During this process, copper (serving as a Lewis acid) may interact with the phenolic oxygen and stabilize the intermediates leading to a smooth transformation.

Table 5. Scope of reaction of 2-nitrobenzaldehydes with phenols to xanthones[a]

Entry	aryl aldehyde	phenol	xanthone	Yield (%)[b],[c]
1	1a	2a	3aa	95 (86)
2	1a	2b	3ab	91 (84)
3	1a	2c	3ac	98 (89)
4	1a	2d	3ad	84 (76)
5	1a	2e	3ae	78 (70)
6	1a	2f	3af	60 (51)
7	1a	2g	3ag	89 (80)
8	1a	2h	3ag	85 (77)
9	1a	2i	3ai	75 (68)
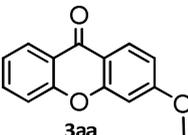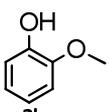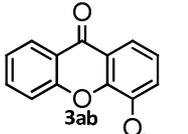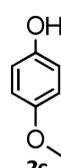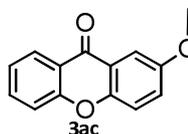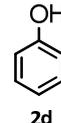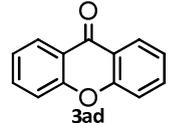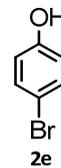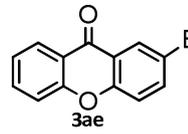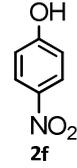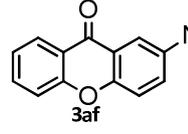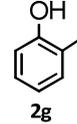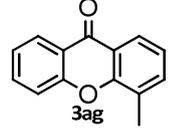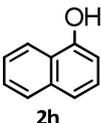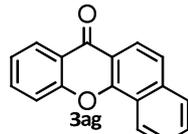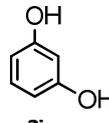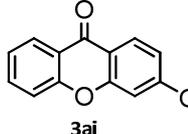
[a] **Reaction conditions:** 2-nitrobenzaldehyde (1 mmol), phenols (1.3 mmol),CuNPs (5 mol %), K_3PO_4 (2.2 eq.), 2 h, under air. [b] Determined by GC using internal standard. [c] Isolated yield (in parentheses).

Conclusions

A new copper-based catalyst composed of CuNPs (ca. 3.0 nm) on nanosized silica coated maghemite proved to be an efficient heterogeneous catalyst for the one-pot synthesis of functionalized xanthones. 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 (no detected by AAS) and the high atom economy involved in the transformations studied, make this methodology to fulfill the requirements of green catalysis. Although the experimental observations point to 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 re-adsorb [13].

The potential scalability of the process and the simple reaction conditions, combined with the low cost of the starting materials makes this methodology transferable to pharmaceutical purposes. Efforts to extend this protocol to other heteroatom-containing compounds and further mechanistic studies are underway.

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