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Facile synthesis of benzofurans *via* copper-catalyzed aerobic oxidative cyclization of phenols and alkynes[†]

Wei Zeng, Wanqing Wu, Huanfeng Jiang,* Liangbin Huang, Yadong Sun, Zhengwang Chen and Xianwei Li

Regioselective synthesis of polysubstituted benzofurans using a copper catalyst and molecular oxygen from phenols and alkynes in a one-pot procedure has been reported. The transformation consists of a sequential nucleophilic addition of phenols to alkynes and oxidative cyclization. A wide variety of phenols and alkynes can be used in the same manner.

Benzofurans are ubiquitous in biologically active molecules¹ and have also been used as building blocks for both heterocyclic and acyclic compounds.² Many efforts have been made to achieve efficient synthesis of these motifs.³ In the past decades, transition metal-catalyzed reactions have emerged as powerful methods for the synthesis of benzofurans,⁴ but simple phenols have rarely been used as starting materials to directly construct these scaffolds.⁵ As common precursors and core structures of chemicals ranging from pharmaceuticals to polymers, phenols are versatile synthetic intermediates and useful reagents for C-H functionalization in organic synthesis.⁶ However, under oxidative conditions, dearomatization of phenols is likely to occur and generate quinol/quinone-derived products.⁷ Such a drawback restricts the application of phenols in the synthesis of heterocyclic compounds via transition metal-catalyzed oxidative cyclizations.

From an economical and environmental viewpoint, catalytic oxidation processes employing molecular oxygen (O_2) or air as a terminal oxidant are extremely valuable and will be more applicable to industrial catalysis. The direct oxidative coupling between two C–H bonds provides a highly attractive strategy for ideal chemical synthesis.⁸ Compared with the methods based on noble-metals, copper–oxygen based methods are obviously economically attractive. The development of copper-catalyzed aerobic oxidative C–H functionalizations leads to new types of synthetic transformations.⁹ Collectively, there are many reports on copper-catalyzed oxidative C–H bond functionalization or nucleophilic/cyclization reactions for the synthesis of heterocycles.¹⁰ Herein, we report a novel and efficient coppercatalyzed sequential nucleophilic addition and oxidative cyclization of easily available phenols and alkynes using O₂ as the oxidant, which provides polysubstituted benzofuran derivatives in moderate to good yields.

Based on our continuing efforts to achieve copper-catalyzed bond formation reactions, nucleophilic additions and homocoupling reactions of alkynes,¹¹ we first studied the reaction of phenols and 1,2-diphenylethyne in PhNO₂ using $CuCl_2 \cdot 2H_2O$ as a catalyst, $ZnCl_2$ as a Lewis acid, and O_2 as an oxidant. The reaction was chosen as a model system to investigate the proposed transformation (Table 1).

Table 1 Optimization of the reaction conditions^a

	1			
○ OH + ○ =		- [Cu], Lewis acid O ₂ balloon Solvent, 100 °C		
1a	2a			3a
Entry	Lewis acid	[Cu]	Solvent	$\operatorname{Yield}^{b}(\%)$
1	ZnCl ₂	CuCl ₂ ·2H ₂ O	PhNO ₂	45
2	$ZnCl_2$	CuBr ₂	$PhNO_2$	50
3	$ZnCl_2$	CuI	$PhNO_2$	54
4	$ZnCl_2$	$Cu(acac)_2$	$PhNO_2$	60
5	$ZnCl_2$	$Cu(OTf)_2$	$PhNO_2$	80
6	$ZnCl_2$	$Cu(BF_4)_2 \cdot 6H_2O$	$PhNO_2$	43
7	AgNO ₃	$Cu(OTf)_2$	$PhNO_2$	40
8	$In(OTf)_2$	$Cu(OTf)_2$	$PhNO_2$	60
9	$Zn(OTf)_2$	$Cu(OTf)_2$	$PhNO_2$	84
10	$ZnCl_2$	$Cu(OTf)_2$	DMSO	—
11	$ZnCl_2$	$Cu(OTf)_2$	DMF	_
12	$ZnCl_2$	$Cu(OTf)_2$	NMP	_
13	$ZnCl_2$	$Cu(OTf)_2$	Xylene	_
14^{c}	$ZnCl_2$	$Cu(OTf)_2$	$PhNO_2$	93
$15^{c,d}$	$ZnCl_2$	$Cu(OTf)_2$	$PhNO_2$	35
16	$ZnCl_2$	_	$PhNO_2$	—
17		$Cu(OTf)_2$	$PhNO_2$	11

^{*a*} Reactions were carried out using **1a** (1.5 mmol), **2a** (1.0 mmol), Lewis acid (1.5 eq.), cat. (10% mol), solvent (2 mL), O_2 , 24 h. ^{*b*} Determined by GC. ^{*c*} Reaction at 120 °C. ^{*d*} Reaction in air.

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China. E-mail: jianghf@scut.edu.cn; Fax: +8620-87112906; Tel: +8620-87112906

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To our delight, the desired benzofuran 3a was obtained in 45% GC yield (Table 1, entry 1). Initial screening revealed that Cu(OTf)₂ was the best choice for this transformation, and other copper salts such as CuBr₂ and CuI were also effective, albeit affording the products with slightly diminished yields (entries 2-5). Use of other conventional Lewis acids as catalysts resulted in far less effectiveness (entries 7 and 8). Though $Zn(OTf)_2$ gave a better yield (entry 9), we chose $ZnCl_2$ as the Lewis acid because it is economically attractive. After solvent evaluation we found that PhNO₂ was the only effective solvent, while no reaction occurred in other solvents (entries 10-13). The temperature was then examined, and it was found that a higher temperature was suitable for this reaction (entry 14). The reaction was less effective when proceeding in air (entry 15). Several control experiments were conducted. Under the standard reaction conditions, no product could be detected in the absence of a copper catalyst (entry 16). Moreover, the transformation was less effective when proceeding without the addition of the Lewis acid (entry 17).



^{*a*} Reactions were carried out using phenols (1.5 mmol), **2a** (1.0 mmol), ZnCl₂ (1.5 eq.), Cu(OTf)₂ (10% mol), PhNO₂ (2 mL), O₂, 24 h. ^{*b*} Isolated yields obtained using flash chromatography.

With the optimized conditions in hand [phenol (1.5 mmol), 1,2-diphenylethyne (1.0 mmol), O₂, ZnCl₂ (1.5 eq.), Cu(OTf)₂ (10% mol), 120 °C, 24 h], we focused on the scope of this transformation. A variety of phenol derivatives were examined and the results are summarized in Table 2. The reaction could be successfully applied to a range of different substituted phenols and gave the corresponding products in moderate to excellent yields. Phenols with either an electron-donating or an electron-withdrawing group on the benzene ring generated the corresponding products in moderate to good yields. Clearly, electronic effects play an important role, as electron-rich substituents (3a-d, 3l, 3m) on the benzene ring favored the transformation. It should be noted that reaction conditions were also compatible with the sulfide group (3n), fluoro, chloro, bromo and iodo substituent groups (3e-3k), which could be used for further reactions. Fortunately, 2-naphthol and arylsubstituted phenols could be successfully generated in this reaction system (30, 3p).

To further demonstrate the efficiency and generality of this process, we then examined the transformation with a range of 1,2-diphenylethyne derivatives under the optimized reaction conditions. As shown in Table 3, with 1,2-diphenylethyne derivatives as starting materials, all the tested reactions proceeded smoothly and afforded the corresponding benzofurans (4a–4f) under the standard conditions. To our delight, when phenylethyne with one alkyl at one side and an aryl group at the other side is used, the desired unsymmetrical products 4g–4i could also be synthesized in this way and showed high regioselectivity. The structure of compound 4i was further confirmed by NOESY analysis (see ESI[†] for details).

On the basis of our experimental data and previous reports,¹² a plausible reaction mechanism for this copper-catalyzed synthesis



^{*a*} Reactions were carried out using **1a** (1.5 mmol), alkynes (1.0 mmol), $ZnCl_2$ (1.5 eq.), $Cu(OTf)_2$ (10% mol), $PhNO_2$ (2 mL), 24 h. ^{*b*} Isolated yields obtained using flash chromatography.



of benzofurans is illustrated in Scheme 1. First, (*E*)-(1-phenoxyethene-1,2-diyl)-dibenzene **A** was generated from an intermolecular nucleophilic addition of phenol **1a** to 1,2-diphenylethyne **2a**, promoted by Cu(π) and Lewis acid. Subsequently, **A** undergoes an intramolecular electrophilic substitution *via* C–H functionalization of the aromatic hydrogen in the presence of the Cu catalyst to give an intermediate **B**, followed by the oxidative cyclization to form a new carbon–carbon bond and afford the final product **3a**.

In summary, we have developed a highly efficient approach for the synthesis of polysubstituted benzofurans *via* coppercatalyzed nucleophilic addition and aerobic oxidative cyclization of phenols and alkynes. It is noteworthy that this method exhibits good functional group tolerance and provides an attractive synthetic strategy for the benzofuran derivatives. Furthermore, the use of readily available starting materials and molecular oxygen as the oxidant makes the overall chemical transformation sustainable and practical. Detailed investigations to understand the reaction mechanism and expansion of the synthetic applications are ongoing in our laboratory.

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