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Cu_2O-Catalyzed Tandem Ring-Opening/Coupling Cyclization Process for the Synthesis of 2,3-Dihydro-1,4-benzodioxins

Weiliang Bao,* Yunyun Liu, Xin Lv, and Weixing Qian

Department of Chemistry, Zhejiang University, Xi Xi Campus, Hangzhou, Zhejiang 310028, P. R. of China

wlbao@css.zju.edu.cn

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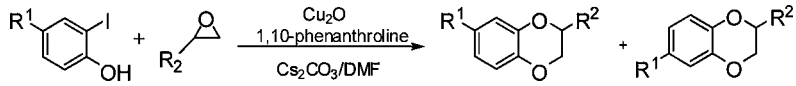
ABSTRACT



2, 3-Dihydro-1, 4-benzodioxins can be prepared in a tandem one-pot procedure by reaction of *o*-iodophenols with epoxides catalyzed by Cu_2O/1, 10-phenanthroline/Cs_2CO_3 system. The reaction is suggested to occur via a novel ring-opening/coupling mechanism, giving moderate to good yields. Moreover, both aryl and aliphatic epoxides are tolerated under these conditions.

Compounds containing 1, 4-benzodioxane structures have attracted considerable interest during the past few years due to their interesting biological activities.[1] For example, fluparoxan (Figure 1, **1**) is claimed to have potent antidepressant properties,[2] the mesylate salt of doxazosin (**2**) is an effective antihypertension agent,[3] piperoxan (**3**), an α-adrenergic blocking agent with considerable stimulating activity, has been used to diagnose pheochromocytoma and served as an antihypertension agent,[4] and WB 4104 (**4**) is recognized as a selective α-adrenoceptor antagonist.[5]Moreover, they are found in a variety of natural products, such as silybin,[6] isosilybin,[7] haedoxan A,[8] eusiderin,[9] purpurenol,[10] and so on.[11] These compounds could also be used as intermediates for further synthetic transformations.[12]

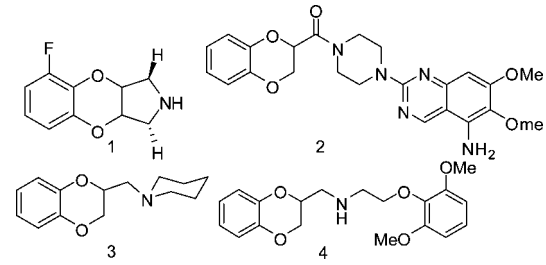


Figure 1. Structures of some biologically important 1,4-benzodioxanes.

Several methods for the assembly of 1,4-benzodioxanes have developed in recent years. One of the typical approaches employs catechols as substrates, which can react with various

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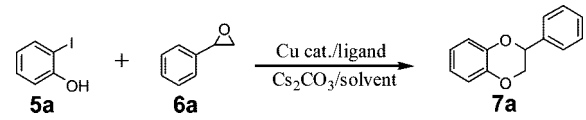
reagents, such as epoxides, α-haloalkene, 1,4-bis(methoxycarbonyloxy)but-2-ene or 3,4-bis (methoxycarbonyloxy)but-1-ene, and so on.[13] Another approach uses the cycloaddition of a variety of *o*-quinones with dienophile, either directly or via a two-step process involving a hetero-Diels−Alder reaction followed by a [3,3] sigmatropic rearrangement.[14] More recently, a method for the synthesis of 1,4-benzodioxans from halo alcohols through a Pd-catalyzed intramolecular etherification has been reported.[15] However, these methods have some limitations with respect to the availability of the starting materials and the higher costs of Pd catalysts, as well as tedious multistep sequence.

Thus, a general and practical method to prepare 1, 4-benzodioxanes is still required.

In the past few years, the formation of aryl C−X bonds (X = N, O, S, etc.) via copper-catalyzed Ullmann coupling between aryl halides and heteroatom-centered nucleophiles has drawn considerable attention.[16] More recently, the Ullmann coupling was successfully extended to the preparation of many heterocycles via copper-mediated cyclization.[17] Li and co-workers reported a copper-catalyzed tandem double-alkenyl C−N bond formation by the reaction of (1*Z*,3*Z*)-1,4-diiodo 1,3-dienes with amides to form di- or trisubstituted *N*-acylpyrroles.[18] Ma and co-workers developed a novel protocol for the elaboration of *N*-substituted 1,3-dihydrobenzimidazol-2-ones from methyl *o*-haloarylcarbamates via a CuI/amino acid catalyzed coupling with amines and subsequent condensative cyclization.[19] Copper-catalyzed tandem C−N bond formation for the synthesis of *N*-alkylbenzimidazoles in regioisomerically pure form starting from *o*-haloanilines has been recently reported by Buchwald and co-workers.[20] The above reports developed a simple and convenient method for synthesis of various heterocycles in an efficient process. Here we would like to describe a new general and practical methodology to synthesize 1,4-benzodioxanes from *o*-iodophenols and epoxides catalyzed by a Cu_2O/1,10-phenanthroline system via cascade ring-opening/coupling cyclization reactions.

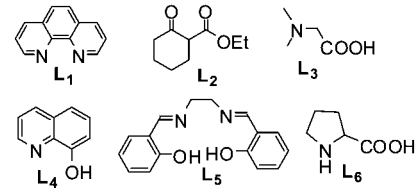
In our initial screening experiment, the reaction of *o*-iodophenol **5a** with styrene oxide **6a** mediated by cesium carbonate was chosen as a model for exploring the suitable reaction conditions (Table 1). It was found that the reaction worked at 90 °C in toluene under the action of 15% CuI and 30% 1,10-phenanthroline giving the corresponding product **7a** (entry 1). Raising the reaction temperature to 110 °C resulted in an improved yield (entry 2). When the copper(I) source was switched to CuBr or Cu_2O, the product yield was enhanced (entries 4 and 5). From an economic point of view, Cu_2O was a better catalyst than CuBr. Several solvents such as toluene, DMSO, NMP, butyronitrile, and DMF were tested. DMF was superior to the other solvents (entries 5−9). A brief study of the effect of the ligand was also carried out; 1,10-phenanthroline $\mathbf{L_1}$ provided good

Table 1. Optimization of Experimental Conditions for **7a**[a]



5a **6a** **7a**

entry	ratio	ligand	catalyst	solvent	temp (°C)	yield (%)[b]
1	1:1	$\mathbf{L_1}$	CuI	PhMe	90	43
2	1:1	$\mathbf{L_1}$	CuI	PhMe	110	48
3	1:1.2	$\mathbf{L_1}$	CuI	PhMe	110	50
4	1:1.2	$\mathbf{L_1}$	CuBr	PhMe	110	53
5	1:1.2	$\mathbf{L_1}$	Cu_2O	PhMe	110	54
6	1:1.2	$\mathbf{L_1}$	Cu_2O	DMSO	110	43
7	1:1.2	$\mathbf{L_1}$	Cu_2O	DMF	110	61
8	1:1.2	$\mathbf{L_1}$	Cu_2O	NMP	110	48
9	1:1.2	$\mathbf{L_1}$	Cu_2O	nC_3H_7CN	110	50
10	1:1.5	$\mathbf{L_1}$	Cu_2O	DMF	110	89
11	1:1.5	$\mathbf{L_2}$	Cu_2O	DMF	110	30
12	1:1.5	$\mathbf{L_3}$	Cu_2O	DMF	110	15
13	1:1.5	$\mathbf{L_4}$	Cu_2O	DMF	110	57
14	1:1.5	$\mathbf{L_5}$	Cu_2O	DMF	110	15
15	1:1.5	$\mathbf{L_6}$	Cu_2O	DMF	110	57



[a] Reaction conditions: CuX (15 mol %), Ligand (30 mol %), Cs_2CO_3 (2 mmol), solvent (2 mL), 48 h, ratio based on *o*-iodophenol. [b] Isolated yield.

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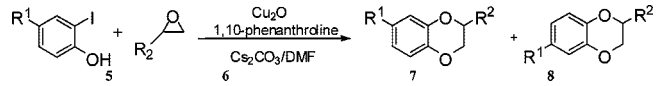
Table 2. Scope of the Sequential One-Pot Ring-Opening/Coupling Protocol[a]



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entry	ortho-iodophenol	epoxide	product	yield[b] (%)/regioisomer ratio (**7:8**)[c]
1	**5a**	**6a**	**7a**	90
2	**5a**	p-Cl-C$_6$H$_4$ **6b**	**7b**	70
3	**5a**	Ph **6c**	**7c**	71
4	**5a**	o-Me-C$_6$H$_4$ **6d**	**7d**	62
5	**5a**	**6e**	**7e**	63
6	t-C$_4$H$_9$ **5b**	**6e**	**7f**	76
7	Cl **5c**	**6e**	**7g**	74
8	H$_3$C **5d**	**6a**	**7h** **8h**	71 (92:8)
9	**5b**	**6a**	**7i** **8i**	75 (87:13)
10	**5c**	**6a**	**7j** **8j**	58 (75:25)
11	**5d**	**6c**	**7k**	68
12	**5b**	**6c**	**7l**	61
13	**5c**	**6c**	**7m** **8m**	57 (78:22)
14	**5b**	**6b**	**7n** **8n**	62 (94:6)
15	**5d**	H$_2$C=HC(H$_2$C)$_6$ **6f**	**7o**	49
16	**5e**	**6a**	**7p** **8p**	81 (75:25)

[a] Reaction conditions: *o*-iodophenol (1 mmol), epoxide (1.5 mmol), Cu_2O (15 mol %), 1, 10-phenanthroline(30 mol %), Cs_2CO_3 (2 mmol), in DMF (2 mL) at 110 °C for 48 h. [b] Isolated yield. [c] The regioisomer ratios were based on NMR spectrum and GC.

catalytic activity in this transformation (entries 9−15). In addition to the solvent and ligand, the ratio of *o*-iodophenol to styrene oxide was found to have a dramatic influence on the reaction outcome (compare entries 2 and 3 as well as entries 7 and 10).

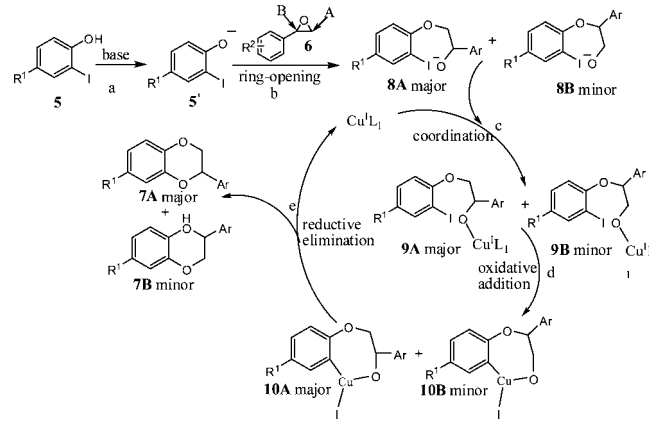
On the basis of the above results, the reaction scope was explored with different epoxides and *o*-iodophenols. As indicated in Table 2, both aryl and aliphatic epoxides could react with *o*-iodophenols giving the corresponding products in moderate to good yield. No spectacular electronic effects were observed when cyclohexene oxide was submitted to reaction with para-substituted *o*-iodophenols (entries 6 and 7). When styrene oxide **6a** and 2-(phenoxymethyl)oxirane **6c** were used as the substrates, the *o*-iodophenols with electron-rich substituents were generally superior to electron-deficient ones, as evidenced by giving better yields (compare entries 8−10 and 16, as well as entries 11−13). This result may be explained by the symmetry of the cyclohexene oxide.

2-(*o*-Tolyloxymethyl)oxirane **6d** proved to be a significantly less effective coupling partner due to its steric hindrance (compare entries 3 and 4). Condensation of substituted *o*-iodophenols with epoxides may afford a single regioisomer or a mixture of two regioisomers. The configuration of the isomers (**7p** and **8p**) was determined by ^{1}H NMR chemical shifts of H_a and H_b on th naphthalene ring (entry 16). Takuwa reported that H_a of **7p** resonated at lower field than H_b of **8p** probably due to a deshielding effect of the phenyl group at the position **2**.[14e] The NMR signals of our products **7p** and **8p** were in very good agreement with the chemical shifts provided by Takuwa, and **7p** was the major regioisomer. The phenate favored to attack the position of epoxide with less steric hindrance under basic conditions.

A plausible mechanism, which accounts for the formation of the 1,4-benzodioxane compounds from the *o*-iodophenols and epoxides, is shown in Scheme 1. First, in the presence of base, the *o*-iodophenol (**5**) transformed into phenate (**5′**)(step **a**), then it would attack onto electrophilic carbons of the styrene oxide **6** (the assault onto the position A would take priority) and the intermediates **8** would be formed (**8A** was major) (step **b**). Coordination of the oxygen to copper to give **9** (**9A** was major), followed by an oxidative addition to **10** (**10A** was major), and then a reductive elimination to release product **7** (**7A** was major) with concomitant regeneration of the catalyst/ligand (step **e**).

In conclusion, we have developed a novel, facile and practical protocol for the synthesis of 1,4-benzodioxanes through a Cu_2O/1,10-phenanthroline-catalyzed tandem ring-opening/coupling cyclization reaction. This method allows the use of a wide range of *o*-iodophenols and epoxides to assemble various products in moderate to good yields. The readily accessible starting materials and relatively mild conditions should provide a useful tool for intramolecular C−O cyclization by copper catalysis in organic chemistry.

Scheme 1. Plausible Mechanism



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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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