Copper-catalyzed tandem process: an efficient approach to 2-substituted-1,4-benzodioxanes†

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An efficient method for the preparation of various 2-substituted-1,4-benzodioxanes by CuBr-catalyzed tandem reactions of 2-((*o*-iodophenoxy)methyl)oxiranes with phenols has been developed. The reaction involves the ring-opening process of 2-((2-iodophenoxy)methyl)oxirane followed by an intramolecular C–O cross coupling cyclization.

Compounds containing 1,4-benzodioxane structures have received special attention in chemical, medicinal and pharmaceutical research, mainly due to their important biological activities and natural occurrence. Presently, there are numerous 1,4-benzodioxane derivatives that have been reported with fantastic bioactivities and some typical examples are outlined in Fig. 1. Spiroxatrine **A**, with a high affinity for serotonin (5-hydroxytryptamine, 5-HT) receptor, has been shown to possess some neuroleptic activity.[1] *N*-Hydroxyureas (**B**) based on the 1,4- benzodioxane template could act as inhibitors of 5-lipoxygenase,[2] while 5-benzylidene-thiazolidine-2,4-dione (**C**) is claimed to have glycogen phosphorylase inhibitor activity.[3] Some derivatives are recognized as α- or β-blocking agents and could be used in antidepression or antihypertension therapy, such as piperoxan (**D**) and so on.[4] More importantly, 1,4-benzodioxane has been found as the central unit in many natural products of meritorious biological functions.[5] Due to their arguable value in biochemical and medicinal researches, 1,4-benzodioxane compounds have also reasonably been widely employed as building blockers for the synthesis of functional heterocyclic compounds.[6]

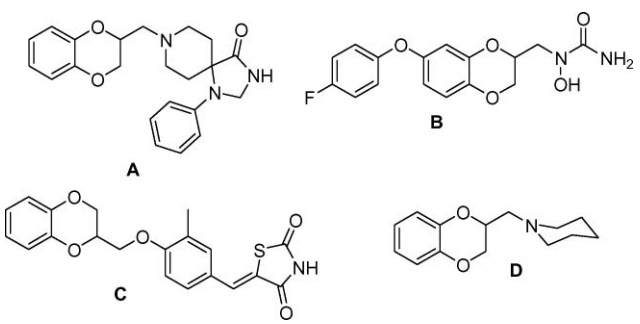
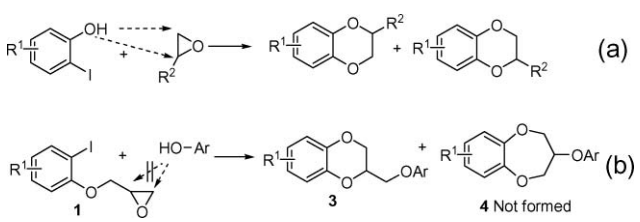


Fig. 1 Structures of some biologically important 1,4-benzodioxanes.

Presently, there are different synthetic methodologies giving access to 1,4-benzodioxanes. One of the most commonly applied methods employs catechol as starting reactant, which furnishes different 1,4-benzodioxane derivatives by incorporating proper electrophilic species such as vicinal dibromides, epihalohydrin, epoxides, α-halo Michael acceptors or bromoketones.[7] The intramolecular cyclization of pyrocatechol monoprop-2-ynyl ethers or intermolecular cyclization of catechol and propargylic carbonates under palladium catalysis also lead to the production of functionalized 1,4-benzodioxanes.[8] The Diels–Alder reaction between *o*-quinone and dienophile is another interesting prototype of constructing 1,4-benzodioxane moiety.[9] These aforementioned synthetic routes, though practical as reported, are just applicable for the preparation of 1,4-benzodioxanes of particular substitution patterns. And some of them suffer from the limitation of low reactant diversity, use of expensive reagents/catalysts or unsatisfactory product yields. In this regard, developing new synthetic methodologies which provide 1,4-dioxones of new functional pattern and involve the use of cheap catalyst as well as readily available starting materials are highly desirable.

During the past few years, the copper-catalyzed coupling reaction between aryl halides and heteroatom-centered nucleophiles for the formation of C–C or C–X (X = N, O, S, *etc.*) bond has been successfully developed during the past few years.[10] Recently, these coupling reactions have displayed versatile applicability in the tandem synthesis of tremendous heterocyclic compounds *via* one-pot operation.[11–13] Typically, the Cu-catalyzed cascade, one-pot reactions for synthesis of indole derivatives,[14,12d] 3,4-disubstituted isoquinolin-1(2*H*)-ones,[12e] *N*-acylpyrroles,[11b] benzoxazoles,[15] 2*H*-1,4-benzoxazin-3-(4*H*)-ones[11c] *etc*. have been successfully developed and turned out to be extremely useful. Our group previously developed a novel Cu-catalyzed cascade reaction to synthesize substituted 1,4-benzodioxanes in one-pot by employing *o*-iodophenol and epoxide as starting materials (Eq a, Scheme 1).[16] This kind of



Scheme 1 Synthesis of 1,4-benzodioxanes *via* different Cu-catalyzed tandem reactions.

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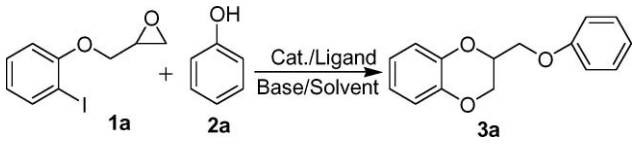
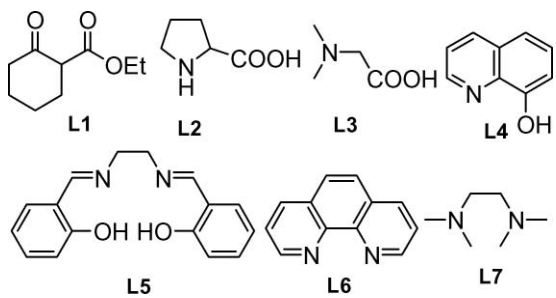
strategy has also later been proved to be applicable for the one-pot synthesis of aza heterocyclic analogs of 1,4-benzodioxanes by other chemists.[17] In despite of the usefulness of this protocol, the formation of two hardly isolable isomers is the key problem in our previous work. Upon the analysis of the reaction, we noticed that the isomer occurs because the nucleophilic phenol is capable of attacking two eletrophilic sites in the epoxide (Eq a, Scheme 1). In order to further improve the regioselectivity of the reaction, we envisioned that limiting the selectivity of nucleophile attack to the sites of epoxide may be effective to achieve this goal; therefore, a new synthetic route has been designed as showing in Eq b (Scheme 1). By elaborating the methylene epoxide group to the *o*-iodidephenol, the functionalized reactant **1** is expected to furnish 1,4-benzodioxanes with considerably higher selectivity in the presence of additional nucleophile and copper catalyst since the formation of another potential isomer with seven-membered heterocyclic structure is not favored by the reaction kinetics. More notably, the 1,4-benzodioxane product **3** provided by this new protocol bears the methylene group, which is the common feature of the most bioactive 1,4-benzodioxane scaffolds (Fig. 1).

In the initial study, 2-((*o*-iodophenoxy)methyl)oxirane **1a** and phenol **2a** were subjected for the desired transformation at the presence of CuI/Cs_2CO_3 and ligand **L1** in DMF, we were glad to find that the target 1,4-benzodioxane **3a** was formed and isolated in 35% yield after 48 h reaction at 110 °C (Table 1, entry 1). This result encouraged us to optimize the reaction parameters to enhance the yield of **3a** on this template reaction. Firstly, some typical ligands frequently used for Cu-catalyzed coupling reactions have been screened. Among the seven selected candidates, 1,10-phenanthroline afforded the highest product yield (entries 1–7). Then, several different Cu(I) catalysts have been respectively tested, it is interesting that CuBr turned out to bear the best catalytic efficiency (entries 6 and 8–10). In the consequent experiments, we evaluated the influence of base additive on the reaction and the results confirmed that Cs_2CO_3 was the most proper choice (entries 6 and 11–15). Finally, a brief study on other related reaction conditions including solvent and reaction temperature were performed, the results implied that using DMA as solvent at 120 °C was able to further enhance the yield of **3a** (entries 16–22). So, the general reaction conditions were established as those used in entry 22 (Table 1).

Table 1 Optimization on reaction conditions for the tandem synthesis of 1,4-benzodioxanes[a]



Entry	Catalyst	Ligand	Solvent	Base	Yield(%)[b]
1	CuI	**L1**	DMF	Cs_2CO_3	35
2	CuI	**L2**	DMF	Cs_2CO_3	Trace
3	CuI	**L3**	DMF	Cs_2CO_3	27
4	CuI	**L4**	DMF	Cs_2CO_3	21
5	CuI	**L5**	DMF	Cs_2CO_3	Trace
6	CuI	**L6**	DMF	Cs_2CO_3	49
7	CuI	**L7**	DMF	Cs_2CO_3	15
8	CuBr	**L6**	DMF	Cs_2CO_3	59
9	CuCl	**L6**	DMF	Cs_2CO_3	51
10	Cu_2O	**L6**	DMF	Cs_2CO_3	53
11	CuI	**L6**	DMF	$K_3PO_4 \cdot 2H_2O$	35
12	CuI	**L6**	DMF	KOH	30
13	CuI	**L6**	DMF	K_3PO_4	37
14	CuI	**L6**	DMF	DBU	NR[c]
15	CuI	**L6**	DMF	K_2CO_3	43
16	CuBr	**L6**	DMSO	K_2CO_3	19
17	CuBr	**L6**	DMA	K_2CO_3	57
18	CuBr	**L6**	DMF	K_2CO_3	46
19	CuBr	**L6**	Xylene	K_2CO_3	49
20	CuBr	**L6**	Toluene	K_2CO_3	51
21	CuBr	**L6**	DMA	Cs_2CO_3	67
22	CuBr	**L6**	DMA	Cs_2CO_3	76[d]

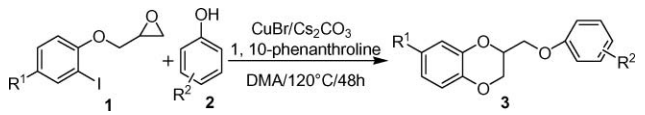


[a] Reaction conditions: Cat. (15 mol%), ligand (30 mol%), base (2 mmol), phenol (1.2 mmol), (2-((*o*-iodophenoxy)methyl)oxirane (1.0 mmol), solvent (2 mL), 48 h, 110 °C. [b] Isolated yield. [c] No reaction. [d] Reaction temperature was 120 °C.

After confirming the obtainable satisfactory yield of this tandem transformation, we were forwarded to investigate the application scope of this new methodology. A class of different (2-((*o*-iodophenoxy)methyl)oxiranes and various phenols have been employed respectively for the reaction. Typical results from this section are summarized in Table 2. As anticipated, all entries in our experiments specifically gave the 1,4-benzodioxane as the product while the isomers of type **4** were not detected. According to the present results, the electronic nature of substituted (2-((*o*-iodophenoxy)methyl)-oxiranes showed no observable influence on the reaction process as both electron-deficient and electron-rich (2-((*o*-iodophenoxy)methyl)oxiranes gave corresponding products in similarly good yields (entries 12 and 16). On the other hand, the property of the substitution group in the phenol exhibited evident effect on the reaction efficiency. Generally, phenol substrates bearing electron donating groups afforded corresponding 1,4-benzodioxanes in higher yields than those bearing electron withdrawing groups (entries 2, 3, 7 and 13, 15). In addition, the substitutions located in the *ortho*- or *meta*-sites also led to slightly lower yield of the product (entries 2, 4, 5 and 13, 14). These results suggest that the nucleophilicity of phenol component directly impact the yield of the final products. The presence of electron-withdrawing groups were tolerated, either at the *para*- or at the *ortho*- position of the phenol (entries 9 and 10). It is also noteworthy that disubstituted phenols and naphthol are also well tolerated to this reaction by providing corresponding 1,4-benzodioxanes in moderate or good yields (entries 6, 8 and 11), which demonstrates the broad application scope of this methodology.

In summary, we have developed a new tandem synthetic routes to the novelly decorated 1,4-benzodioxanes. The reaction involves in a cascade process of nucleophilic ring-opening and CuBr-catalyzed intramolecular coupling transformation. All reactions

Table 2 Scope of the sequential one-pot ring-opening/coupling protocol[a]



Entry	R^1	R^2	Product/yield[b]
1	H	H	**3a**/76
2	H	*p*-Me	**3b**/79
3	H	*p*-*t*-Bu	**3c**/80
4	H	*m*-Me	**3d**/77
5	H	*o*-Me	**3e**/73
6	H	2,4-di-*t*-Bu	**3f**/70
7	H	*p*-Cl	**3g**/69
8	H	2,4-di-Cl	**3h**/57
9	H	*o*-$COCH_3$	**3i**/56
10	H	*p*-CHO	**3j**/61
11	H	**2k**/naphthol	**3k**/59
12	Me	H	**3l**/79
13	Me	*p*-Me	**3m**/81
14	Me	*m*-Me	**3n**/77
15	Me	*p*-Cl	**3o**/71
16	Cl	H	**3p**/73

[a] Reaction conditions: (2-((*o*-iodophenoxy)methyl)oxirane (1 mmol), phenol (1.2 mmol), CuBr (15 mol%), 1,10-phenanthroline(30 mol%), Cs_2CO_3 (2 mmol), in DMA (2 mL) at 120 °C for 48 h. [b] Isolated yield.

were performed using simple and cheap materials while the products were obtained with considerably increased molecular complexity as well as a typical structural feature of known biofunctional scaffolds. More importantly, through the modification on the reactant structure, the problem of producing isomers *via* the nuleophilic attack to different sites of epoxide has been successfully avoided in the present study. Therefore, this methodology is not only a highly useful route for the synthesis of 1,4-benzodioxane derivatives, but also a guide for improving similar reactions which suffers from the undesirable regio-sites reactions. Further study on expanding the application of this system to the synthesis of analogous heterocycles is presently in progress in our lab.

Experimental

General procedure for the synthesis of 2-substituted-1,4-benzodioxanes

A Schlenk tube was charged with CuBr (22 mg, 15% mol), 1,10-phenanthroline (57 mg, 30% mol), Cs_2CO_3 (650 mg, 2 mmol), phenol (113 mg, 1.2 mmol), evacuated and backfilled with nitrogen. Then 2-((2-iodophenoxy)methyl)oxirane (276 mg, 1.0 mmol), DMA (2 mL) were successively added. The reaction tube was quickly sealed and the contents were stirred at 120 °C for 48 h. Then the cooled reaction mixture was dissolved in H_2O and extracted with Et_2O. The combined organic layer was dried ($MgSO_4$). The product was further purified by column chromatography (silica gel, PE-EtOAC).

2-Phenoxymethyl-2,3-dihydrobenzo[1,4]dioxin (3a). White solid, m.p. 35–36 °C[3]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, J = 7.6 Hz, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.96–6.90 (m, 6H), 4.59–4.56 (m, 1H), 4.43 (dd, J = 1.4, 11.4 Hz, 1H), 4.30–4.22 (m, 2H), 4.19–4.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.26, 143.18, 142.91, 129.55, 121.74, 121.53, 121.40, 117.40, 117.25, 114.56, 71.34, 66.24, 65.34; IR: υ = 3019, 2930, 2882, 1578, 1493, 1269, 1237, 1076, 745, 689 cm^{-1}.

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