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COMMUNICATION

Direct synthesis of enaminone functionalized biaryl ethers by CuI-catalyzed *O*-arylation of enaminone functionalized phenols†

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The *O*-arylation of *o*-enaminone functionalized phenols, namely, (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-ones, has been achieved *via* a self-promoted process in the presence of CuI, which provided a class of new biaryl ethers bearing a reactive enaminone fragment. The reactions were performed under mild conditions and the functionalized biaryl ether products have been found as useful building blocks for the assembly of heterocyclic compounds.

The Ullmann-type C–O coupling reaction is one of the most widely employed strategies for creating C–O bonds which link aryl or other unsaturated carbons. The application of the traditional Ullmann protocol is limited by harsh reaction conditions (up to 200 °C) and the use of stoichiometric amounts of copper catalyst.[1–2] Numerous efforts have been made in recent decades in order to eliminate the harsh conditions. Palladium catalysts have been found to be capable of mediating the transformation under mild conditions, but large scale application is also limited by the high cost of palladium catalysts.[3–5] In this regard, searching for appropriate copper catalyst systems is still a central topic in the research of Ullmann coupling reactions. An interesting discovery is that nanoparticle copper catalysts are significantly better catalysts than equivalent copper species of normal size in catalyzing these reactions,[6–9] however, nanoparticle catalysts also suffer from the problem of high cost. Presently, employing a ligand to activate the conventional low-cost commercial copper catalysts (CuX, Cu_2O, CuO *etc.*) is the most popular strategy in these reactions. Using C–O coupling reactions, various molecules such as biaryl ethers,[10–12] oxazoles,[13] benzoxazoles,[14] xanthones,[15] benzodioxines,[16] benzoxazines,[17] to name but a few, have been sucessfully synthesized *via* copper catalysis with the assistance of ligand. Biaryl ether is a substructure of special interest due to its frequent occurrence in biologically functional molecules with pharmaceutical activities,[18–19] natural products,[20] as well as functional materials.[21]

Although the use of ligands is currently the foremost option for satisfactory C–O coupling reactions, problems such as the additional cost of ligand, tedious isolation processes and the production of chemical waste have arisen since ligands are usually used as additives and not recycled in most cases. On the other hand, presently known C–O couplings still rely on harsh conditions in the absence of a ligand. For example, Sperotto[22] *et al.* reported the ligand-free synthesis of biaryl ethers by reacting phenols and aryl halides in NMP at 160 °C; Chan[23] *et al.* achieved the same transformation by refluxing DMF and using nBu_4NBr as an additive and aryl iodides as aryl halides. To reconcile the contradiction between harsh reaction conditions and the impact brought by the ligand, a theoretically applicable tactic is making use of the internal chelating effect of the reactants or solvents themselves to carry out the coupling reactions under mild conditions *via* self-promotion. A typical example of the type in C–O coupling has been reported by Ma and coworkers. In their experiments, an *ortho*-NHCOR substituted aryl halide successfully reacted with phenols to give the corresponding biaryls under very mild conditions. The *ortho*-NHCOR group was believed to provide important chelating assistance during the coupling reactions.[24]

During our research in developing practical C–X coupling methodologies, we have discovered that (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one **1a** is an efficient ligand for copper-catalyzed Ullmann-type coupling reactions of aryl halides with *N*-heterocycles[25] and tandem reactions of thiophenols with aryl halides.[26] During further investigation on **1**, we discovered that they are able to undergo self *O*-arylation to furnish enaminone functionalized biaryl ethers in the presence of a copper catalyst without using any additional ligand. Considering the interest of both biaryl ethers and enaminone moieties,[27–30] we envisioned that a self-promoted C–O coupling method for the synthesis of these biaryl ethers functionalized by an enaminone fragment might be useful. Herein we wish to report our preliminary results on the self-promoted C–O coupling reactions of enamiones **1** with aryl halides to synthesize new biaryl ether derivatives under mild conditions.

The initial study was carried out based on the model reaction between enaminone functionalized phenol **1a** and iodide benzene **2a**. Optimization results are summarized in Table 1. First, the effect of different bases was studied. Among the screened bases, Cs_2CO_3 exhibited the best promotion effect (Table 1, entries 1–7).

As for solvents, both DMF and DMSO displayed an inferior mediating effect (Table 1, entries 8–9). Using an excess of phenol **1a** was also attempted, but the yield of **3a** was not enhanced (Table 1, entry 10). However, 1.5 eq mol of iodobenzene led to a higher yield of **3a** (Table 1, entries 11–12). Finally, prolonging the reaction time to 24 h significantly increased the yield of **3a**, while no further

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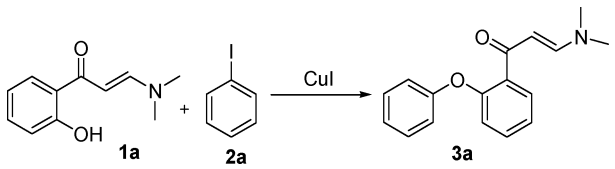
Table 1 Optimization of the reaction conditions[a]



Entry	Base	Solvent	Time (h)	Yield (%)[b]
1	K_2CO_3	CH_3CN	12	29
2	*t*-BuOK	CH_3CN	12	10
3	K_3PO_4	CH_3CN	12	—[c]
4	KOH	CH_3CN	12	<5
5	$NaHCO_3$	CH_3CN	12	—
6	$(CH_3CH_2)_3N$	CH_3CN	12	—
7	Cs_2CO_3	CH_3CN	12	43
8[d]	Cs_2CO_3	DMF	12	—
9[d]	Cs_2CO_3	DMSO	12	—
10[e]	Cs_2CO_3	CH_3CN	12	42
11[f]	Cs_2CO_3	CH_3CN	12	38
12[g]	Cs_2CO_3	CH_3CN	12	48
13[g]	Cs_2CO_3	CH_3CN	24	61
14[g]	Cs_2CO_3	CH_3CN	36	59

[a] Unless otherwise specified, the general reaction conditions are: phenol **1a** (0.5 mmol), iodobenzene **2a** (0.6 mmol), 10 mol% CuI and 2 eq base refluxed in CH_3CN (5 mL) under N_2 atmosphere. [b] Isolated yield based on **1a**. [c] No product was obtained. [d] The reaction temperature was 100 °C. [e] Overdosed **1a** (0.6 mol) was used to react with **2a** (0.5 mmol). [f] The ratio of **1a** : **2a** was 1 : 1 mol. [g] 0.75 mmol Iodobenzene was used.

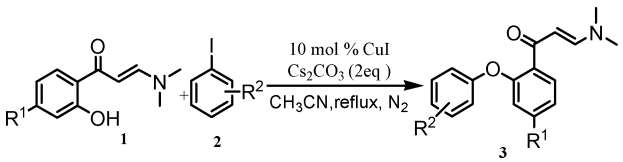
enhancement was observed when the reaction time is prolonged to 36 h (Table 1, entries 13–14). Therefore, the parameters shown in entry 13 were chosen as the optimum conditions for further studies.

The scope of this transformation was then investigated under optimized reaction conditions. First, various iodobenzene derivatives were reacted with different enaminone functionalized phenols **1** (Table 2). It was found that iodobenzenes containing either electron withdrawing or electron donating groups tolerated the coupling reactions well and provided corresponding biaryl ethers with different phenols **1**. As expected, iodobenzene having electron withdrawing substitutions gave slightly better yields (Table 2, entries 1–5), while the *o*-CF_3 substituted iodobenzene gave a fair result (Table 2, entry 6). Phenols **1** with different substitution groups similarly provided fair to good yields of products (Table 2, entries 7–14).

Next, the application scope of this methodology was further extended to the reactions of aryl bromides. The obtained results are shown in Table 3. Based on the results, aryl bromides are also capable of serving as aryl donors to yield the corresponding biaryl ethers **3**, but the efficiency of the reaction is generally lower than that of aryl iodides. Similarly to aryl iodide reactions, 3-fluoro phenol **1c** gave generally lower yields of products than the unsubstituted phenol **1a** and 3-methoxy phenol **1b** (Table 3, entries 1, 2, 4, 6 *vs.* 7, 8, 10, 13 and 14, 17, 16, 18). On the other hand, compared to the full carbon aryl bromide, 2-bromopyridine exhibited significantly superior reactivity and gave excellent yields of biaryl ethers **3s**, **3y**, and **3ac** (Table 3, entries 6, 13 and 18). All the products were clearly characterized by ^1H, ^{13}C NMR as well as HRMS.

In order to examine the potential of biaryl ethers **3** as building blocks in the synthesis of heterocyclic compounds, **3a**

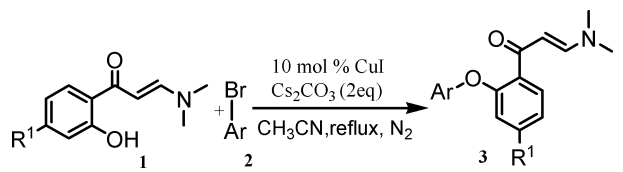
Table 2 Synthesis of various enaminone functionalized biaryl ethers[a]



Entry	R^1	R^2	Product	Yield (%)[b]
1	H	H	**3a**	61
2	H	4-Cl	**3b**	77
3	H	4-Br	**3c**	61
4	H	4-Me	**3d**	65
5	H	4-MeO	**3e**	57
6	H	3-CF_3	**3f**	36
7	MeO	H	**3g**	80
8	MeO	4-Cl	**3h**	67
9	MeO	4-Br	**3i**	78
10	MeO	4-Me	**3j**	57
11	MeO	4-MeO	**3k**	60
12	F	4-Cl	**3l**	65
13	F	4-Br	**3m**	62
14	F	H	**3n**	41

[a] Reaction conditions: Phenol **1** (0.50 mmol) and iodobenzene **2** (0.75 mmol), 10 mol % CuI and 1.0 mmol Cs_2CO_3 refluxed in 5 mL MeCN for 24 h. [b] Isolated yield based on **1**.

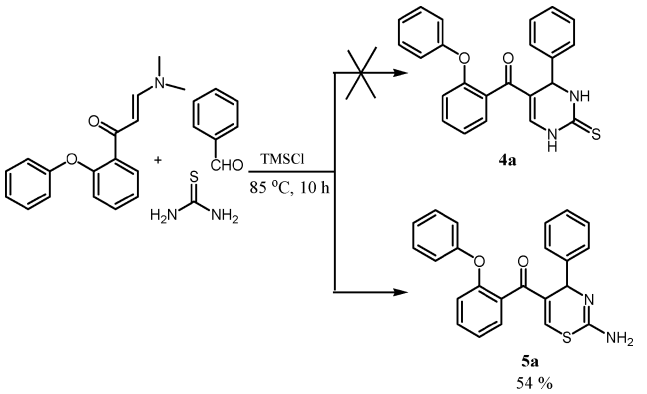
Table 3 Synthesis of enaminone functionalized biaryl ethers from aryl bromides[a]



Entry	R^1	Ar	Product	Yield (%)[b]
1	H	Ph	**3a**	55
2	H	4-FC_6H_4	**3o**	50
3	H	4-AcC_6H_4	**3p**	39
4	H	2-MeC_6H_4	**3q**	54
5	H	Naphth-2-yl	**3r**	43
6	H	Pyridin-2-yl	**3s**	75
7	MeO	H	**3g**	41
8	MeO	4-FC_6H_4	**3t**	62
9	MeO	4-AcC_6H_4	**3u**	60
10	MeO	2-MeC_6H_4	**3v**	45
11	MeO	3-$NO_2C_6H_4$	**3w**	63
12	MeO	Naphth-2-yl	**3x**	37
13	MeO	Pyridin-2-yl	**3y**	96
14	F	H	**3l**	30
15	F	4-AcC_6H_4	**3z**	40
16	F	2-MeC_6H_4	**3aa**	39
17	F	4-FC_6H_4	**3ab**	45
18	F	Pyridin-2-yl	**3ac**	68

[a] Reaction conditions: Phenol **1** (0.50 mmol) and bromobenzene **2** (0.75 mmol), 10 mol % CuI and 1.0 mmol Cs_2CO_3 refluxed in 5 mL MeCN for 24 h. [b] Isolated yield based on **1**.

was subjected to a three-component reaction with benzaldehyde and thiourea. Unexpectedly, the three-component reaction did not give the dihydropyrimidinone product **4a** as in the case of conventional enaminones in our previous study.[29] Instead, the isomeric heterocycle 1,3-thiazine **5a** was obtained as a single product (Scheme 1). This result suggested that the biaryl fragment



Scheme 1 Regioselective three-component synthesis of 1,3-thiazine using biaryl ether **3**.

in the structure of **3a** evidently modified the reactivity of this enaminone synthon. This result also implies that biaryl ethers **3** are useful for the regioselective synthesis of new heterocyclic products. Further studies on the general applications of enaminone functionalized nucleophiles initiated coupling reactions as well as the regioselective three-component reactions involving **3** are presently ongoing in our laboratory.

In summary, we have developed the first self-promoted O-arylation reaction of enaminone functionalized phenols. This transformation was practical for both aryl iodides and bromides in reflux acetonitrile. The biaryl ether products displayed novel regioselective reactivity by producing 1,3-thiazine heterocyclic compounds in multicomponent reaction. This coupling method is useful for the synthesis of these new biaryl ethers and further demonstrated the function of the enaminone backbone as a ligand in C–X coupling reactions.

Experimental section

Typical procedure for the synthesis of biaryl ethers 3

A 25 mL round bottom flask was charged with 0.50 mmol of phenol **1** and 0.05 mmol of CuI. Then, 0.75 mmol of aryl halide and 1.0 mmol of Cs_2CO_3 were added. The mixture was stirred for 24 h under N_2 in refluxing MeCN (5 mL). After cooling down to room temperature, 5 mL of water was added, and the product was extracted with EtOAc (10 mL × 3). The combined organic layers were dried overnight over anhydrous Na_2SO_4. Subsequently, the organic solvent was removed *in vacuo* after filtration. The residues were purified by silica gel column chromatography to afford the corresponding product **3**.

Three-component synthesis of 1,3-thiazine 5a

In a 25 mL round bottom flask, 0.3 mmol of **3a**, 0.3 mmol of benzaldehyde and 0.36 mmol of thiourea were dissolved in 2 mL DMF. Then, 0.45 mmol of TMSCl was injected into the flask and the reaction was stirred for 10 h at 85 °C. After completion of the reaction, 5 mL of water was added and the product was extracted with EtOAc (8 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and evaporating the organic solvent, the residue was purified by silica gel column chromatography to afford **5a**.

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