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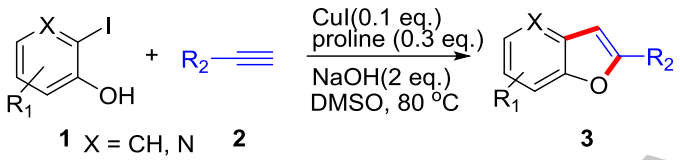

1 X = CH, N **2** **3**

Copper catalyzed, noble metal free
Coupling-annulation domino raction
24 exmaples, upto 96 % yield.
Broad diversity of substrate scope.

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ABSTRACT

CuI/Proline-catalyzed coupling reaction of 2-iodo-phenols with terminal alkynes and the following cyclization process is carried out successively in DMSO at 80 °C. Under this tandem process, 2-substituted benzo*[b]*furans/furo-pyridines were synthesized in good to excellent yields with a great diversity.

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Substituted benzo*[b]*furans are ubiquitous structural units in many natural products and pharmaceutical synthetic intermediates. [1, 2] For example, the 2-substituted benzo*[b]*furan moiety is found in **Bufuralol**, [3] a novel antihypertensive agent and (+)-**machaeriol B**, an antimicrobial and antimalarial agent.[4] A series of structures containing the 2-aryl-benzo*[b]*furan nucleus, such as **SKF-63058**, have been identified as potential multifunctional drugs for Alzheimer's disease (**Figure 1**).[5]

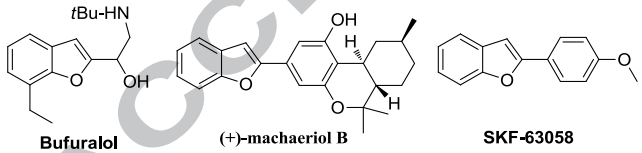
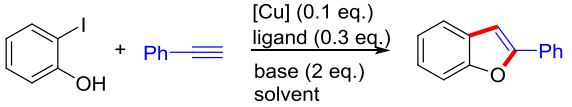


Figure 1 Biologically active 2-substituted benzo*[b]*furans.

Therefore, the development of general and efficient methodologies for the synthesis of benzo*[b]*furans is highly desired. Among the various methods developed over the years, [6,7] the processes that including transition metal catalyzed Sonogashira coupling of 2-halophenols with terminal alkynes, followed by intra-molecular cyclization, have been frequently used to construct 2-substituted benzo*[b]*furans. [7]

Our strategy for the synthesis of 2-substituted benzo*[b]*furans is based on the early report of Stevensons, R. et al [6t] and Ma et al, [8] the former found that cuprous acetylides could react with 2-halophenols to give benzofurans. Ma and colleagues developed a method that allowed the formation of the multi-substituted indoles by the CuI/Amino acid catalyzed Sonogashira coupling and tandem coupling-annunlation procedure.

Table 1. Optimization of the reaction conditions for the model reaction [a]



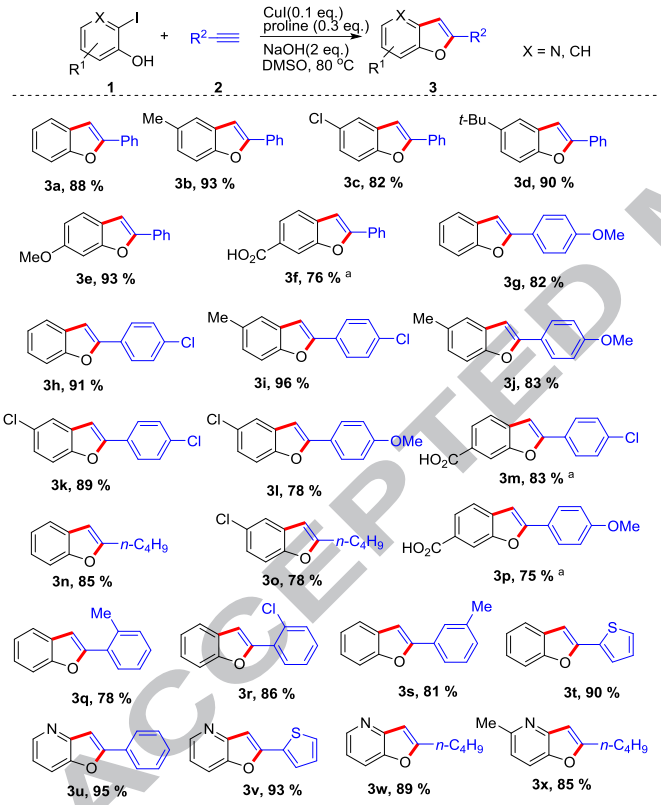
1a **2a** **3a**

Entry	[Cu]	ligand	base	solvent	Yield [b]
1	CuI	Proline	K_2CO_3	DMF	55 %
2	CuBr	Proline	K_2CO_3	DMF	28 %
3	CuCl	Proline	K_2CO_3	DMF	15 %
4	Cu_2O	Proline	K_2CO_3	DMF	12 %
5	CuO	Proline	K_2CO_3	DMF	/
6	CuI	*N*-methylglycine	K_2CO_3	DMF	41 %
7	CuI	*N,N*-dimethylglycine	K_2CO_3	DMF	35 %
8	CuI	Glycine	K_2CO_3	DMF	27 %
9	CuI	PPh_3	K_2CO_3	DMF	8%
10	CuI	1,10-Fenanthrolin	K_2CO_3	DMF	26%
11	CuI	dppm	K_2CO_3	DMF	13%
12	CuI	Proline	Na_2CO_3	DMF	29 %
13	CuI	Proline	Cs_2CO_3	DMF	37 %
14	CuI	Proline	K_3PO_4	DMF	41 %
15	CuI	Proline	NaOH	DMF	78 %
16	CuI	Proline	KOH	DMF	70 %
17	CuI	Proline	LiOH	DMF	61 %
18	CuI	Proline	NaOH	DMSO	88 %
19	CuI	Proline	NaOH	NMP	56 %
20	CuI	Proline	NaOH	EtOH	20 %
21	CuI	Proline	NaOH	Pyridine	/
22	CuI	Proline	NaOH	Toluene	/
23	CuI	Proline	NaOH	Dioxane	62 %

[a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), base (2 mmol), CuX (0.1 mmol), ligands (0.3 mmol), solvent (5 mL), sealed tube, N^2, 80 °C, 12 h.
[b]Isolated yield.

At the outset, 2-iodophenol **1a** and phenylacetylene **2a** were selected as model coupling reaction partners to screen the conditions (Table **1**). Initially, a series of copper salts were investigated, it has been found that cuprous salt was more reactive than the cupric analogue (entries 4, 5). Among all the tested cuprous salts, CuI was the most effective, forming the title product **3a** in 55 % yield (entry 1). Then, different additives were added, Proline displayed more reactive in this reaction (entries 1, 6-11). Furthermore, various bases were screened (entries 1, 12-17) to identify the optimized condition, NaOH was superior to the others, affording **3a** in 78 % yield (entry 15). Finally, the effect of the solvents were examined, we found that polar aprotic solvents were more suitable (entries 15, 18, 19, 23), and DMSO seems to be the best choice (88 %, entry 18). However, when pyridine or toluene was used as the solvent, no product was observed in the reaction system (entries 21, 22).

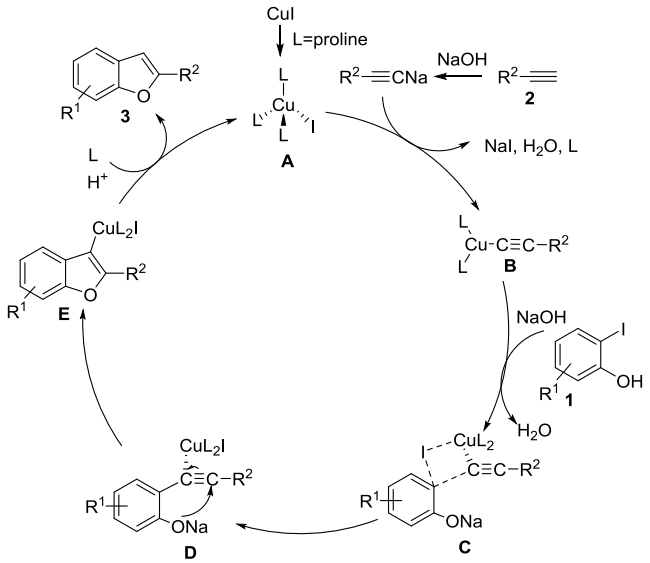
Under the optimized reaction conditions, 2-iodophenols **1** and 1-alkynes **2** underwent the transformation smoothly, producing desired 2-substituted benzo*[b]*furans or furo-pyridines **3** in good to excellent yields. The results are illustrated in Scheme **1**.



Scheme 1 Substrate scope of 2-iodophenols **1** and 1-alkynes **2**. Reaction conditions: **1** (1 mmol), **2** (1 mmol), NaOH (2 mmol), CuI (0.1 mmol), Proline (0.3 mmol), DMSO (5 mL), sealed tube, N_2, 80 °C, 12h. [a] 3 mmol NaOH was added.

Firstly, several commercially available substituted 2-iodophenols **1** were used to react with phenylacetylene **2a** under the optimized reaction condition. 2-iodophenols with electron-donating and electron-withdrawing groups could all connected with phenylacetylene **2a** smoothly, to form the desired 2,5- or 2,6-disubstituted products (Scheme **1**, **3a-3f**). The results further revealed that electron-donating groups such as 4-methyl, 4-tertbutyl or 5-methoxyl of the 2-iodophenol could improve the yield from 88 % (**3a**) to 93 % (**3b**), 90 % (**3d**) and 93 % (**3e**), respectively. But electron-withdrawing groups, for example 4-chloro or 5-carboxyl, were less effective, affording the desired compounds in 82 % (**3c**) and 76 % (**3f**) yield. Then, various 1-alkynes were tested, both aromatic and aliphatic alkynes could reacted with 2-iodophenols successfully, affording the corresponding multi-substituted benzo*[b]*furans (**3g-3t**) with good to excellent yield. These results demonstrated that aromatic alkynes with electron-withdrawing groups could give a positive effect to the reaction, comparing (**3a**, **3h**), (**3b**, **3i**), (**3c**, **3k**) and (**3f**, **3m**). On the other side of the coin, electron-donating groups gave us a little lower yield, comparing (**3a**, **3g**), (**3b**, **3j**), (**3c**, **3l**) and (**3f**, **3p**). A series of *ortho*- and *meta*- substituted phenylethynes then coupled with 2-iodophenol **1a** to form benzo*[b]*furan **3q**, **3r** and **3s**, respectively. We were pleased to found that when the aliphatic alkyne such as hex-1-yne was treated with substituted 2-iodophenols in the general reaction condition, the desired product could also be gained in good yields(**3n**, **3o**). Heteroaryl alkyne, such as 2-ethynylthiophene was well compatible to this tandem reaction system, when reacted with 2-iodophenol **1a**, giving 2-(thiophen-2-yl)benzo*[b]*furan **3t** with 90 % yield. When ortho-iodo-pyridinols were used to couple with different kind of terminal alkynes,such as phenylacetylene, 2-ethynylthiophene and hex-1-yne under the standard reaction condition, the corresponding 2-substituted furo-pyridines could be gained with high yields (Scheme **1**, **3u-3x**).

A proposed mechanism for the present reaction is then illustrated in Scheme **2**. (1) Alkyne **2** was deprotoned and reacted with CuI-Proline complex **A** to form copper acetylide **B** by the releasing of one eq. Ligand[9]; (2) **B** was inserted to deprotoned aryl iodide **1** to form a four-centered transition state **C**; (3) **C** was then converted to the phenolate **D** to furnish the formal oxdative addtion. (4) By the addtion of the phenolate to the C-C triple bond, the cyclized copper complex **E** was then obtained; (5) Protonolysis of intermediate **E** and the in situ capture of a Ligand formed benzo*[b]*furan **3** and regenerated the active catalyst specy **A** to finish the catalyzed cycle.



Scheme 2 Proposed mechanism for the synthesis of 2-substituted benzo*[b]*furan **3**

In conclusion, a novel and facile route for the synthesis of 2-substituted benzo*[b]*furan/furo-pyridines via a tandem Sonogashira coupling -annulation sequence of 2-iodo-phenols

and terminal alkynes was developed. The reactions were carried out successively in DMSO at 80 °C to provide the corresponding 2-substituted benzo*[b]*furans in good to excellent yields with a great diversity. Further investigation on the application of this strategy is currently underway in our lab.

Acknowledgment

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10. The **experimental procedures and characterization data** for compound **3a**. A sealable reaction tube equipped with a magnetic stirrer bar was charged with 2-iodophenol **1a** (1 mmol), phenylacetylene **2a** (1 mmol), NaOH (2 mmol), CuI (0.1 mmol), Proline (0.3 mmol) and DMSO (5 mL), the reaction vessel was placed in an oil bath at 80 °C under N_2. After stirring the mixture at this temperature for 12 h, it was cooled to room temperature and diluted with ethyl acetate, washed with water and brine, dried over by $MgSO_4$. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel to afford **3a** (171 mg, 88 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 7.3 Hz, 1H), 7.32-7.27 (m, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.00 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.04, 155.03, 130.61, 129.35, 128.86, 128.61, 125.04, 124.35, 123.03, 121.00, 111.26, 101.41. ESI-MS *m/z*: 195.2$(M+1)^+$. HRMS calcd for $C_{14}H_{10}NaO$ $(M+Na)^+$ requires 217.0629, found 217.0635.

1. A one-pot synthetic process of 2-substituted benzo*[b]*furan/hetero-benzo*[b]*furan
2. Starting from 2-iodo-phenol and 1-alkynes
3. Catalyzed by CuI/proline in mild condition, Palladium and Phosphorus free.

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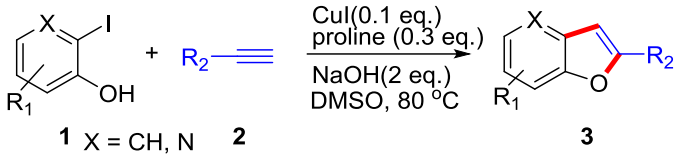

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