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New domino approach for the synthesis of 2,3-disubstituted benzo[*b*]furans via copper-catalyzed multi-component coupling reactions followed by cyclization

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ABSTRACT

An efficient domino process for the construction of 2,3-disubstituted benzo[*b*]furans has been developed via copper-catalyzed three-component coupling reactions of salicylaldehydes, amines, and alkynes followed by base-assisted O-annulation reaction.

1. Introduction

The benzo[*b*]furans are important heterocyclic compounds, which not only act as key structural subunits in naturally occurring compounds that exhibit remarkable biological activities but also represent useful building blocks in the synthesis of natural products.[1] Consequently, much attention has been paid to the development of new methodologies for their preparation. The synthetic strategies for the construction of benzo[*b*]furans mainly are dehydrative cyclization of (α-(phenoxy)-alkyl ketones,[2] decarboxylation of *o*-acylphenoxyacetic acids or esters,[3] [3,3]-sigmatropic rearrangement of various arenes,[4] palladium-catalyzed cyclization of the corresponding 2-(1-alkynyl)phenols,[5] etc.[6] However, most of the methods reported were multi-step operations and lacked generality. It is very attractive to develop an efficient protocol for the synthesis of benzo[*b*]furan derivatives from readily accessible starting materials and in a one-pot procedure. On the other hand, multi-component coupling reactions have received much consideration in synthetic organic chemistry recently.[7] This strategy allows the formation of several bonds including new C–C, C–O and C–N bonds in the same vessel. Especially the three-component coupling reactions of aldehydes, amines, and alkynes (A^3 Coupling) to propargyl amines mediated or catalyzed by Cu,[8] Ag,[9] Au,[10] Ru/Cu,[11] and Ir[12] were well documented. Other procedures promoted by microwave[13] and ultrasound[14] were also disclosed. It could be envisioned that, if the *o*-hydroxy-benzaldehydes were employed in the A^3 Coupling reaction, a sequential intramolecular nucleophilic attack of the oxygen to the triple bond of the propargyl amine intermediate might occur to furnish the benzo-fused heterocycles in one pot. Herein, we wish to report an efficient domino process leading to 2,3-disubstituted benzo[*b*]furans via copper-catalyzed three-component coupling reactions of various salicylaldehydes, amines, and alkynes, followed by base-assisted intramolecular C–O bond formation.

To optimize the process, we first investigated the coupling reactions of salicylaldehyde (**1a**), morpholine (**2a**), and phenylacetylene (**3a**) using 20 mol % CuI as catalyst. It was found that the propargylic amine derivative **4a** was produced in 84% yield by stirring at 110 °C for 3 h in toluene (Table 1, entry 1). However, **4a** did not undergo cyclization under the Cu-catalyzed conditions. It might due to the low nucleophilicity of the hydroxy group attached to the benzene ring. We considered that generation of a phenoxide ion may facilitate nucleophilic attack to the triple bond. Thus, K_2CO_3 and Bu_4NBr were added to the reaction mixture. To our delight, the intermediate of **4a** could be smoothly cyclized to afford 4-(2-benzyl-benzofuran-3-yl)-morpholine **5a** in 85% isolated yield (Table 1, entry 2). It was confirmed that both K_2CO_3 and Bu_4NBr are essential for this one-pot cyclization (Table 1, entries 3, 4). Decreasing the amount of CuI resulted in the yield decreasing considerably (Table 1, entry 5). When K_2CO_3 was reduced to 1.0 equiv, the yield of the desired product was similar to that of 3.0 equiv.

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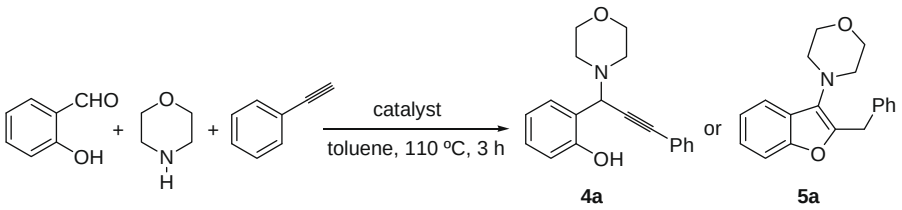
Table 1
Screening of the reaction conditions



4a **5a**

Entry	Catalyst	K_2CO_3 (equiv)	Bu_4NBr (equiv)	Product	Yield[a] (%)
1	20 mol % CuI	None	None	**4a**	84
2	20 mol % CuI	3.0	1.0	**5a**	85
3	20 mol % CuI	1.0	None	**4a**	—[b]
4	20 mol % CuI	None	1.0	**4a**	—[b]
5	10 mol % CuI	1.0	1.0	**5a**	46
6	20 mol % CuI	1.0	1.0	**5a**	81
7	20 mol % CuI	1.0	1.0	**5a**	69[c]

[a] Isolated yields, the ratio of aldehyde:morpholine:acetylene is 2.0:1.0:1.5.
[b] Observed by TLC.
[c] 1.5 equiv of salicyaldehyde was used.

After a brief survey of the experimental conditions as shown in Table 1, it was clear that the optimized reaction condition was to use 20 mol % CuI as the catalyst, 1.0 equiv K_2CO_3 as the base combined with 1.0 equiv Bu_4NBr in toluene at 110 °C.

Having established an effective catalytic system for the one-pot benzo[*b*]furan-forming reaction, we next utilized a variety of salicylaldehydes, amines, and alkynes to explore the scope of this novel cascade A^3-coupling-annulation reaction under the optimal conditions. The representative results are shown in Tables 2 and 3. Although similar reactions were reported,[15,16] the alkynes employed were limited to those aliphatic alkynes bearing a heteroatom, such as propargyl alcohols or propargyl amines, and in most cases, only dihydrobenzofurans were obtained. First, various types of amine substrates were examined (Table 2, entries 1–4). When piperidine (**2b**) was used, the corresponding benzofuran **5b** was obtained in 79% yield (Table 2, entry 2). Dibenzylamine (**2c**) and *N*-benzyl-butylamine (**2d**) were also compatible for this reaction, generating the corresponding benzofurans **5c** and **5d** in 70% and 51% yields, respectively (Table 2, entries 3 and 4). It should be noted that while the current system is quite effective for secondary amines, however, the substrates of primary amine such as $PhNH_2$ could not afford the desired benzofuran. Substituted salicylaldehydes **1b**–**d** cyclized smoothly to afford the corresponding **5e**–**g** in 64–86% yields, and the functionalities of –Cl, –Br, and $–NO_2$ were tolerated well during the reactions (Table 2, entries 5–7). Likewise, when 2-hydroxy-1-naphthaldehyde (**1e**) was employed, the desired product **5h** was obtained in 61% yield (Table 2, entry 8). The scope of this reaction was further examined by applying the optimized conditions to various alkynes. It was found that the aryl alkynes bearing electron-withdrawing or electron-donating group were all effective for the cyclization, furnishing the desired benzofurans **5i** and **5j** in 56% and 75% yields, respectively (Table 2, entries 9 and 10). It is noted that in these cases, a stepwise addition of copper catalyst and K_2CO_3/Bu_4NBr was required to achieve the better yields. Interestingly, when pyridylacetylene was employed, the reaction proceeded smoothly with salicylaldehyde and piperidine or dibenzylamine to produce **5k** and **5l** in 46–69% yields (Table 2, entries 11 and 12). The structure of benzofurans was further confirmed by X-ray crystallographic analysis of **5b**.

In addition to aryl-substituted alkynes, alkyl-substituted alkynes were submitted to the optimized reaction conditions. However, the reaction of 1-octyne with salicylaldehyde and morpholine resulted in no formation of the coupling product even after 6 h. Fortunately, when CuI was changed to CuCN under the similar reaction conditions, it uneventfully gave rise to benzofuran **5m** in 33% yield, along with 30% dihydrobenzofuran **6** (Table 3, entry 1). It should be noted that also in this case, CuCN and K_2CO_3/Bu_4NBr were added stepwise. It is important to first achieve CuCN-catalyzed A^3 Coupling reactions before base-assisted cyclization. Other alkyl-substituted alkynes bearing a heteroatom such as 1-(prop-2-ynyl)-1*H*-indole (**3f**), *N*,*N*-diphenyl-prop-2-ynyl-amine (**3g**), and *N*-methyl-*N*-phenyl-prop-2-ynyl-amine (**3h**) reacted with **1a** and **3a** smoothly to furnish the desired benzofurans **5n**–**p** in good yields (Table 3, entries 2–4).

In conclusion, we have successfully established a highly efficient and general synthetic method for 2,3-disubstituted benzo[*b*]furans via a copper-catalyzed A^3 Coupling/annulation sequence. A number of functional groups such as chloro, bromo, nitro, amino, and pyridyl groups are tolerated under the reaction conditions to provide structurally interesting benzo[*b*]furans in moderate to high yields. Further studies to extend the scope of synthetic utility leading to diverse heterocyclic compounds are in progress in our laboratory.

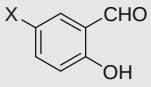
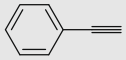
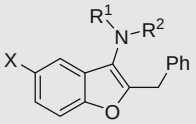
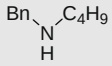
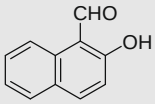
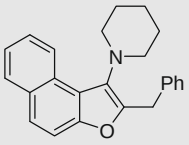
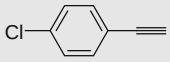
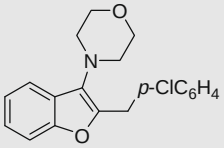
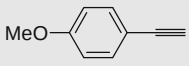
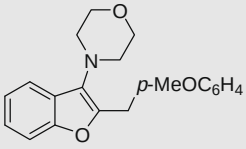
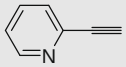
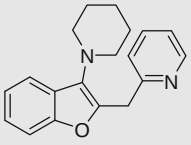
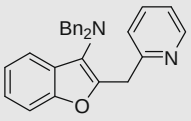
2. Experimental

2.1. General procedure for the preparation of benzo[*b*]furan derivative 5a through CuI-catalyzed multi-component coupling reactions

A mixture of CuI (0.038 g, 0.2 mmol), K_2CO_3 (0.138 g, 1.0 mmol), Bu_4NBr (0.32 g, 1.0 mmol), salicylaldehyde (0.20 mL, 2.0 mmol), phenylacetylene (0.17 mL, 1.5 mmol), and morpholine (0.087 mL, 1.0 mmol) in toluene (5mL) was heated at 110 °C for 3 h. Then the reaction mixture was filtered through Celite and washed with ethyl acetate. After removal of the solvent, the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (10:1) as eluent, affording compound **5a** as a light yellow solid in 81% yield. Alternatively, after the reaction was complete, the reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel.

4-(2-benzyl-benzofuran-3-yl)-morpholine (**5a**), mp 105–108 °C. ^1H NMR ($CDCl_3$, Me_4Si) δ 3.16 (dd, J = 4.5, 4.8 Hz, 4H), 3.83 (dd, J = 4.5, 4.8 Hz, 4H), 4.15 (s, 2H), 7.15–7.37 (m, 8H), 7.63–7.66 (m, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 32.23, 52.54, 67.66,

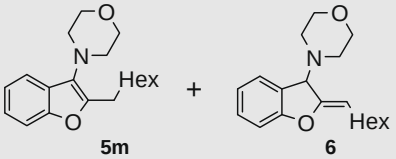
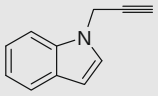
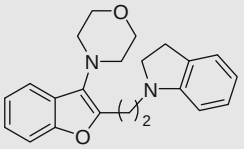
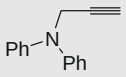
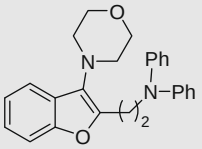
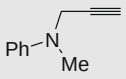
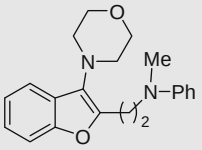
Table 2
Preparation of benzofuran derivatives from salicylaldehydes, acetylenes, and amines

Entry	Aldehyde	Amine	Alkyne	Product	Yield[a] (%)
					
1	X = H, **1a**	**2a**	**3a**	X = H, **5a**	81
2	**1a**	 **2b**	**3a**	X = H, **5b**	79
3	**1a**	 **2c**	**3a**	X = H, **5c**	70
4	**1a**	 **2d**	**3a**	X = H, **5d**	51
5	X = Cl, **1b**	**2a**	**3a**	X = Cl, **5e**	64
6	X = Br, **1c**	**2a**	**3a**	X = Br, **5f**	86
7	X = NO_2, **1d**	**2a**	**3a**	X = NO2, **5g**	86
8	 **1e**	**2b**	**3a**	 **5h**	61
9	**1a**	**2a**	 **3b**	 **5i**	56[b]
10	**1a**	**2a**	 **3c**	 **5j**	75[b]
11	**1a**	**2b**	 **3d**	 **5k**	69
12	**1a**	**2c**	**3d**	 **5l**	46

[a] Isolated yields. The ratio of aldehyde:amine:acetylene is 2.0:1.0:1.5. Unless noted, all the reactions were carried out using 20% CuI, 1.0 equiv K_2CO_3, and 1.0 equiv Bu_4NBr at 110 °C for 2–3 h.

[b] Reaction conditions: 20% CuI, 110 °C, 3 h, then 1.0 equiv K_2CO_3 and 1.0 equiv Bu_4NBr, 110 °C, 1 h.

Table 3
Preparation of benzofuran derivatives from alkyl alkynes

Entry	Aldehyde	Amine	Alkyne	Product	Yield[a] (%)
1	**1a**	**2a**	 **3e**	 **5m** + **6**	33[b]
2	**1a**	**2a**	 **3f**	 **5n**	61
3	**1a**	**2a**	 **3g**	 **5o**	50
4	**1a**	**2a**	 **3h**	 **5p**	68

[a] Isolated yields. The ratio of aldehyde:amine:acetylene is 1.0:1.2:1.5. Reaction conditions: (i) 20% CuCN, rt 1 h, 110 °C, 4–9 h, in toluene. (ii) 1 equiv K_2CO_3, 1 equiv Bu_4NBr, 110 °C, 3 h.
[b] A dihydrofuran of (Z)-4-(2-heptylidene-2,3-dihydro-benzofuran-3-yl)-morpholine **6** was also isolated in 30% yield.

111.65, 119.86, 122.04, 123.43, 126.02, 126.43, 128.50, 128.70, 138.13, 150.19, 153.43. HRMS (EI) for $C_{19}H_{19}NO_2$: calcd 293.1416, found 293.1428.

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Supplementary data

Experimental details and spectroscopic characterization of all new compounds and X-ray crystal structure of compounds **5b** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.204.

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