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Copper-mediated alkylation of furan and thiophene derivatives with cyclic ethers

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ABSTRACT

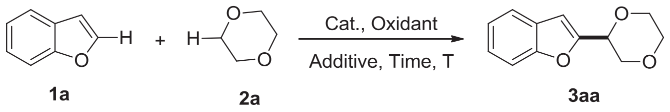
An efficient and complementary copper-catalyzed alkylation of (benzo)furans/(benzo)thiophenes with cyclic ethers was reported. A broad range of C2 heteroaryl-substituted cyclic ethers were obtained in moderate to good yields. The results of control experiments indicated that this transformation might proceed via a radical process.

1. Introduction

The five- or six-membered cyclic ethers widely exist in natural and non-natural products including ligands, nucleosides, annonaceous acetogenins and macrolides.[1] Owing to their chemical stability, the direct construction of cyclic ethers onto other molecules is still a challenging task. Recently, the cross-dehydrogenative coupling (CDC) reaction has become a strategy to generate more complex molecules due to its high atom-economy, easy operation and environment friendly.[2] Using this methodology, the direct C–H activation of simple ethers with different reaction candidates (such as alkanes,[3] olefins,[4] alkynes,[5] carboxylic acids,[6] alcohols[7] and heteroarenes[8]) has been successfully achieved. However, the application of heteroarenes into this transformation was mainly limited to (benzo)azoles,[8a–c] (benzo)thiazoles,[8d] indoles,[8e,8f] pyridines and quinolones.[8g] Although furans and thiophenes are important building blocks that frequently appear in organic synthesis,[9] the alkylation with simple ethers were rarely explored. Only one example of CDC reaction was related to the conversion of benzofuran with 1,4-dioxane.[8f] Therefore, to develop an efficient and complementary protocol via direct C–H alkylation of (benzo) furans/(benzo)thiophenes with cyclic ethers is highly desirable. On the basis of our previous work,[10] herein we report an atom economic copper-catalyzed oxidative CDC reaction of (benzo)furans/(benzo)thiophenes with cyclic ethers.

2. Results and discussion

Initially, the direct alkylation of benzofuran (**1a**) with 1,4-dioxane (**2a**) was carried out in the presence of $Cu(OAc)_2$ (10 mol %), KI (20 mol %) and DTBP (3 equiv) at 120 °C. A relatively low but promising isolated yield 41% of desired product **3aa** was observed (Table 1, entry 1). Increasing the catalyst loading to 20 mol %, the yield achieved to 63% (Table 1, entry 2). Other copper salts could not improve the product yield, except CuI (Table 1, entries 3–6). It was found that di-*tert*-butyl peroxide (DTBP) was the best oxidant, and KI was more efficient additive (Table 1, entries 7–14). The alkylation could not proceed smoothly at lower temperature (Table 1, entry 15). In addition, the structure of **3aa** in crystalline state was established by X-ray diffraction analysis.



Having established optimal reaction conditions, the substrate scope of this copper-catalyzed alkylation of heteroaryls with 1,4-

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Table 1
Optimization of the reaction conditions[a]

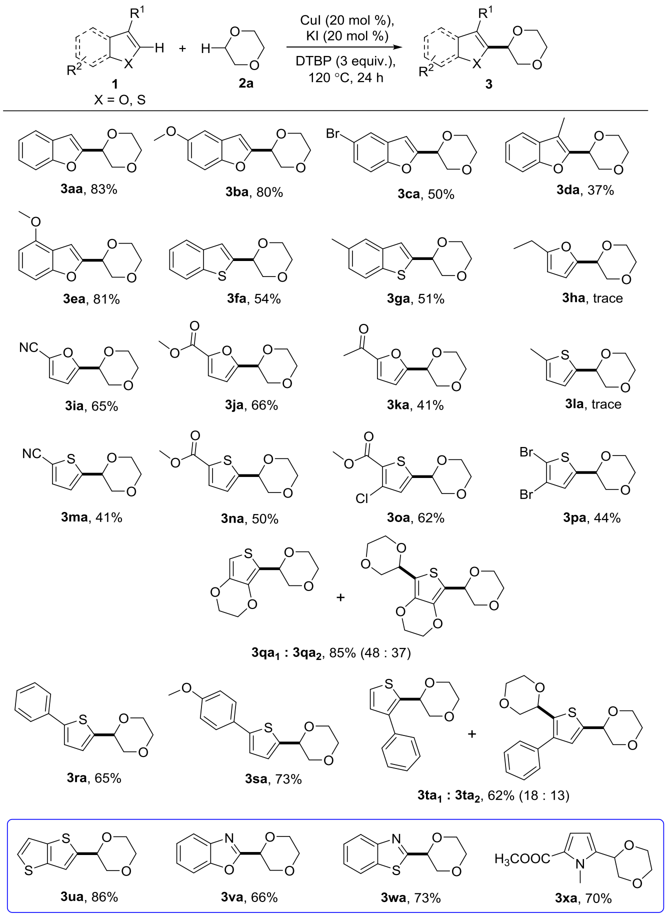
Entry	Catalyst	Oxidant	Additive	Yield/%[b]
1	$Cu(OAc)_2$	DTBP	KI	41
2	$Cu(OAc)_2$	DTBP	KI	63
3	$CuBr_2$	DTBP	KI	55
4	**CuI**	**DTBP**	**KI**	**83**
5	CuCl	DTBP	KI	63
6	CuBr	DTBP	KI	42
7	CuI	TBHP (5–6 M in decane)	KI	Trace
8	CuI	Dicumyl peroxide	KI	Trace
9	CuI	Benzoyl peroxide	KI	Trace
10	CuI	DTBP	NaI	45
11	CuI	DTBP	TBAI	22
12	CuI	DTBP	PPh_3	40
13	CuI	DTBP	Xphos	51
14	CuI	DTBP	—	43
15	CuI	DTBP	KI	51[c]

The values in bold represent the optimized conditions for the studied reaction.
[a] Reaction conditions: **1a** (0.25 mmol), catalyst (10–20 mol %), additive (20 mol %), oxidant (3 equiv), 1,4-dioxane (1.5 mL), in a sealed tube under N_2 at 120 °C (oil bath) for 24 h.
[b] Isolated yield.
[c] 110 °C.

dioxane was investigated (Scheme 1). In general, all tested heteroaryls were able to tolerate this catalyzed system, affording the desired products in mediate to good yields. 4- or 5-Methoxybenzofurans were smoothly transformed into the corresponding products **3ba** and **3ea** in good yields. Only 50% of 5-bromobenzofuran was converted into product **3ca**. Despite the steric hindrance of 3-methylbenzofuran, the desired product **3da** was also isolated in 37%. Comparing with benzofuran (**1a**), the reaction activity of benzothiophenes **1f** and **1g** was decreased, and the target products **3af** and **3ag** were generated in moderate yields. In addition, furans and thiophenes with electron-withdrawing groups (–CN, –COOMe, –COMe and halogen) could smoothly proceed this alkylation to give the corresponding products (**31a**–**3ka**, **3ma**–**3pa**) in satisfactory yields. However, only a trace amount of products were detected from the reaction of furan/thiophene with electron-rich groups (**3ha** and **3la**). Aryl substituted thiophenes reacted with 1,4-dioxane to give **3ra** and **3sa** in moderate yields. The substrates containing two reactive-sites (**1q** and **1t**) could be transformed into mono- and di-substituted products with moderate to high conversation (**3qa$_1$**, **3qa$_2$**, **3ta$_1$** and **3ta$_2$**). To expand the scope of this methodology, the direct alkylation of other heterocycles (such as dithiophene, benzothiazole, benzoxazole and pyrrole) with 1,4-dioxane were explored, giving the corresponding coupled products **3ua**–**3xa** in 86%, 66%, 73% and 70%, respectively.

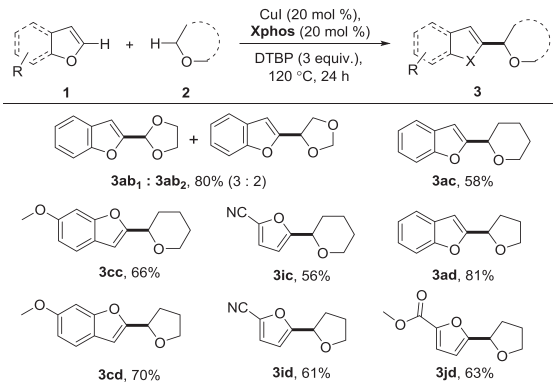
It was found that the standard reaction conditions for 1,4-dioxane were not suitable for other cyclic ethers (such as 1,3-dioxolane, tetrahydro-2*H*-pyran and tetrahydrofuran). Surprisedly, these cyclic ethers could smoothly react with (benzo)furans in the presence of Xphos. Under the modified reaction conditions, 1,3-dioxolane, tetrahydro-2*H*-pyran and tetrahydrofuran (THF) were well tolerated to afford the corresponding targets in moderate to good yields (Scheme 2). 1,3-Dioxolane (**3b**) could be smoothly transformed into C2- and C4-substituted mixture with 80% combined yield (**3ab$_1$** and **3ab$_2$**).

To gain insights into the mechanism of this transformation, some control experiments were performed using THF under the modified conditions (Scheme 3). The strong deuterium kinetic isotope effect ($K_{H/D}$=3.3) indicated that the C(sp^3)–H bond cleavage of THF might be the rate-determining step. When 2.0 equiv of TEMPO was added as a radical inhibitor, no target product was obtained. Two strong molecular ion peaks (*m*/*z*=228.1963 and *m*/*z*=539.2869) were detected and attributed to [TEMPO-THF+H]$^+$ (Exact mass: 228.1958) and [Cu-Xphos]$^+$ (*m*/*z*=539.2869). In order to further clarify the role of the copper salt, the complex of CuI-Xphos was synthesized at 120 °C in THF (analyzed by ESI-MS). The target product could be obtained in a higher yield 90% with this copper salts as a catalyst. This result indicates the following: 1) a radical process might be involved in this reaction; 2) complex [CuI-Xphos] may be the catalytically active species.



[a] Reaction conditions: **1a** (0.25 mmol), catalyst (20 mol %), additive (20 mol %), oxidant (3 equiv.), 1,4-dioxane (1.5 mL), in a sealed tube under N_2 at 120 °C (oil bath) for 24 h, isolated yield.

Scheme 1. Regiospecific C2 coupling of heterocycles with 1,4-dioxane.[a]



[a] Reaction conditions: **1a** (0.25 mmol), catalyst (20 mol %), additive (20 mol %), oxidant (3 equiv.), cyclic ethers (1.5 mL), in a sealed tube under N_2 at 120 °C (oil bath) for 24 h, isolated yield.

Scheme 2. Regiospecific C2 coupling of heterocycles with inactive C(sp^3)–H bond.[a]