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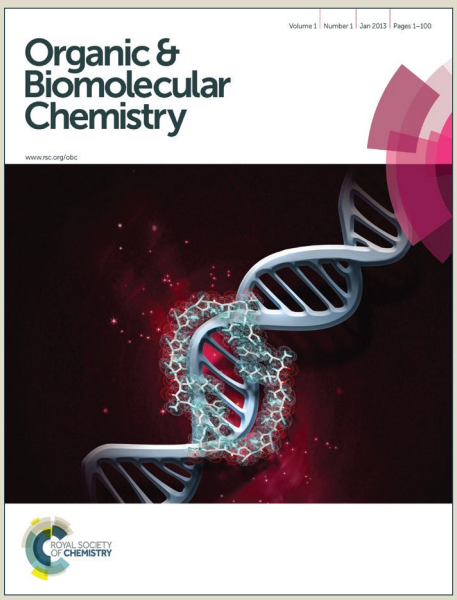

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Intramolecular Oxidative Coupling: I_2/TBHP/NaN_3-mediated Synthesis of Benzofuran Derivatives

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A novel intramolecular oxidative coupling reaction is established to prepare benzofuran derivatives via direct C(sp^2)–H functionalization for the formation of C–O bond. This transformation is mediated by I_2/TBHP/NaN_3 under metal-free conditions and catalytic amount of NaN_3 plays a crucial role in the reaction. Further, the reaction shows a broad substrate scope with middle to excellent yields.

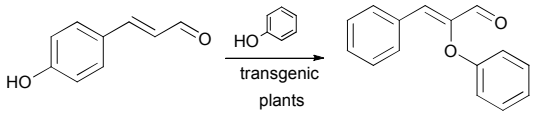
Oxidative coupling reaction is a novel strategy to construct C–C bond[1] and C-heteroatom bond[2], which avoids pre-functionalization of easily available chemicals while improving the atom economy and step economy and has received significant interest over the last ten years. Especially, the efficient construction of useful heterocyclic compounds by using oxidative coupling reaction is an important research area in organic synthesis.[3] Numerous methods have been developed for carbon-heteroatom bond formation in last decades.[4] It is well-known that traditional oxidative coupling reactions are most dependent on transition metal catalyst. As a result, residual transition metal contaminant seriously limits their applications. Consequently, an economical, environmentally friendly and metal-free strategy is drawing many chemists' attention.[5]

Benzofuran and their derivatives are the core structure of many clinical drugs and natural products, which have attracted the exploration of their synthesis methods. Molecules containing these structural units have been shown to exhibit activities against cancer, plasmodium falciparum and so on.[6] Series of methods for the synthesis of benzofuran derivatives have been reported.[7] However, investigation on direct C-H functionalization and C-O bond formation of benzofuran derivatives remains rare.

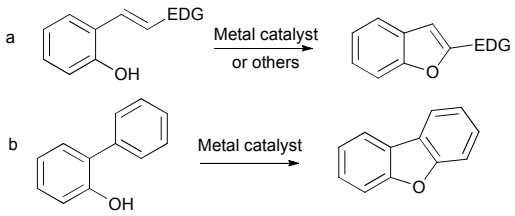
To date, a lot of novel strategies of C-H functionalization and C-O bond formation via oxidative coupling make a big breakthrough.[8] However, there are extreme conditions in oxidative coupling reaction with phenolic hydroxyl due to phenols are ready to undergo oxidative dearomatization to yield quinones.[9] To our best knowledge, oxidative C(sp^2)-H functionalization and C-O bond formation with phenolic hydroxyl generally falls into one of the following types. Type I, early in 2000, Boudet and his co-workers[10] revealed that 4-hydroxycinnamyl aldehydes incorporate into lignins by examining transgenic plants via intermolecular radical coupling reactions (Scheme 1). And authors think that this process appears to reflect simple chemical coupling propensities. Type II, Alessandra Lattanzi[11] and Duan[12] separately developed a new strategy for the synthesis of benzofuran derivatives via C(sp^2)-O coupling reaction(Type II, a). However, their methods are only efficient for electron-rich systems. Later, liu[13], Yoshikai[14] and Zhu[15] reported Pd or Cu catalyzed C(sp^2)-H functionalization of 2-arylphenols via oxidative cyclization respectively (Type II, b). At present, there is no report describing intramolecular oxidative functionalization of electron-deficient systems for preparing benzofuran derivatives under metal-free conditions. Accordingly, exploration of this novel oxidative coupling methods is still of great significance.

Previous work

Type I Intermolecular C(sp^2)-H bond functionalization and C-O bond formation

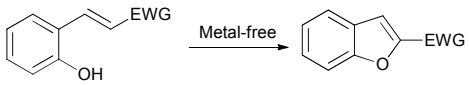


Type II Intramolecular C(sp^2)-H bond functionalization and C-O bond formation



This work

Intramolecular C(sp^2)-H bond functionalization and C-O bond formation

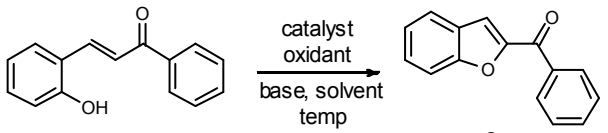


Scheme 1 Different kinds of C-H Functionalization

Recently, I_2 (iodine) system[16] has received considerable attention as a mild, non-toxic and selective reagent in organic synthesis. As a continuous study on the direct C-H functionalization and C-O bond formation, we herein describe an efficient I_2-catalyzed intramolecular oxidative coupling reaction of 2-hydroxychalcones under metal-free conditions. In addition, catalytic amount of NaN_3 plays a crucial role in the oxidative

coupling reaction and a new plausible mechanism which may be virtually through C(sp^3)-H functionalization has been proposed.

Table 1 Optimization of the Reaction Conditions[a]



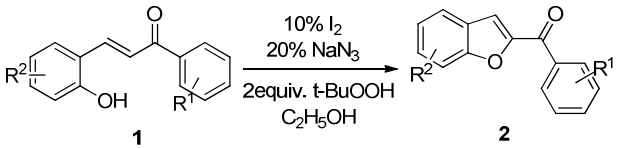
1a **2a**

Entry	Oxidant	Additive	Solvent	Catalyst	Yield[b]
1	TBHP[c]	NaN_3	CH_3CN	I_2	40
2	/	NaN_3	CH_3CN	I_2	NO
3	TBHP	/	CH_3CN	I_2	NO
4	TBHP	NaN_3	CH_3CN	/	NO
5	Others[d]	NaN_3	CH_3CN	I_2	NO
6	TBHP	Others[e]	CH_3CN	I_2	NO
7	TBHP	NaN_3	CH_3NO_2	I_2	NO
8	TBHP	NaN_3	DCE	I_2	NO
9	TBHP	NaN_3	dioxane	I_2	NO
10	TBHP	NaN_3	CH_3CN[f]	I_2	60
11	TBHP	NaN_3	toluene	I_2	20
12	TBHP	NaN_3	C_2H_5OH	I_2	87
13	TBHP	NaN_3[g]	C_2H_5OH	I_2	87
14	**TBHP**	**NaN_3[h]**	**C_2H_5OH**	**I_2**	**88**
15	TBHP	NaN_3[h]	C_2H_5OH	Others[i]	NO
16	TBHP	NaN_3[h]	C_2H_5OH	KI	78
17	TBHP	NaN_3[h]	C_2H_5OH	TBAI	83

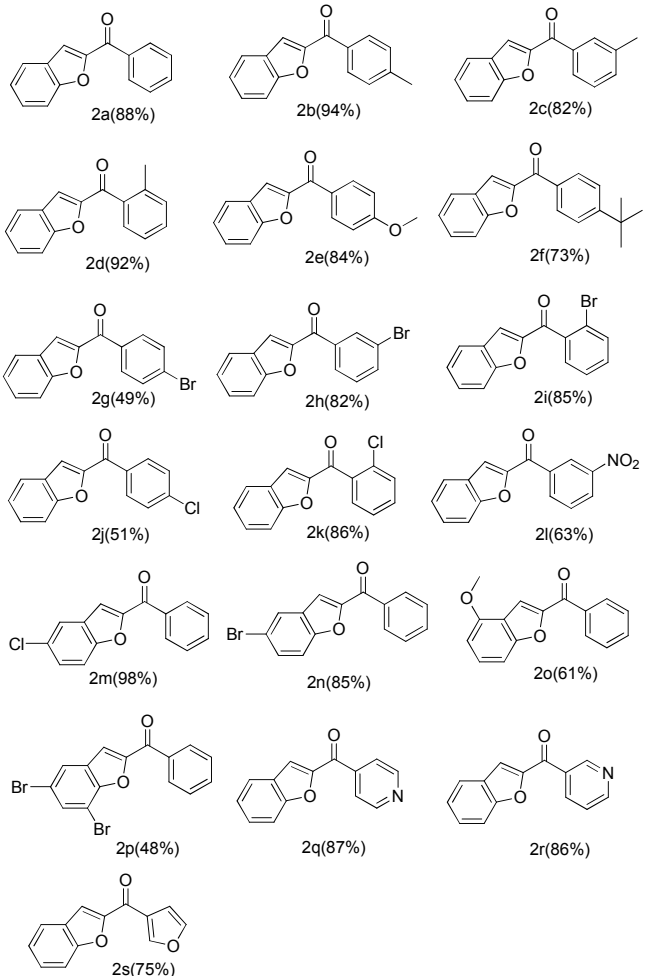
[a]Reaction conditions: **1a** (0.25 mmol), oxidant (0.5 mmol), additive (1 mmol) and catalyst (0.025 mmol) in solvent (4.0 mL) at 80℃, unless otherwise stated. [b]Isolated yields. NO means that no product was observed. [c]All TBHP (70% in water). [d]Other oxidants include PIDA, mCPBA, $K_2S_2O_8$, DTBP. [e]Other additives include K_2CO_3, Na_2CO_3, $NaHCO_3$, NaOH, $NaH_2PO_4{\cdot}2H_2O$, KH_2PO_4, $K_3PO_4{\cdot}3H_2O$, KSCN, $(NH_4)_3PO_3{\cdot}3H_2O$. [f]CH_3CN:H_2O=1:1. [g]2.0 equivalent of NaN_3 was used. [h]0.2 equivalent of NaN_3 was used. [i]Other acids include p-TSA, $BF_3{\cdot}Et_2O$, TfOH, $FeCl_3$, $CuCl_2$.

Initially, trans-2-hydroxychalcone (**1a**, 0.25 mmol) was used as the model substrate for the synthesis of desired product (**2a**). As shown in table 1, **2a** was obtained in 40% yield in the presence of catalytic amount of I_2 (iodine), 0.5 mmol TBHP (tert-butylhydroperoxide, 70% in water) and 1 mmol NaN_3 (Table 1, entry 1). In the absence of I_2, TBHP or NaN_3, no product was obtained (Table 1, entries 2-4). To further optimize the conditions, different oxidants, additives and catalysts were tested. Employing other oxidants: PIDA (iodobenzene diacetate), mCPBA (m-chloroperoxybenzoic acid), $K_2S_2O_8$ or DTBP (tert-butyl peroxide), unfortunately, yielded no product (Table 1, entry 5). Using other additives instead of NaN_3, we also did not observe desired product (Table 1, entry 6). Solvent screening showed that EtOH, MeCN/H_2O, and toluene were also effective for the reaction, while DCE and 1,4-dioxane were ineffective for the reaction (Table 1, entries 7-12). Decreasing NaN_3 to 0.5 mmol made no difference to the yield (Table 1, entry 13). Catalytic amount of NaN_3 (0.05 mmol) was employed out of concern that NaN_3 could be recycled in reaction process and, as expected, target product was obtained in good yield (Table 1, entry 14). In addition, when I_2 was replaced by other acids, including $CuCl_2$, $FeCl_3$, $BF_3{\cdot}Et_2O$, p-TSA and TfOH, no product was observed (Table 1, entry 15). What's more, when KI or TBAI (tetrabutylammonium iodide) was used, the desired coupling product **2a** was also obtained in the yield lesser than I_2 as the catalyst (Table 1, entries 16 and 17). On the basis of these results, the optimized reaction conditions were concluded to be 0.1 equivalent of I_2, 0.2 equivalent of NaN_3 and 2.0 equivalent of TBHP in C_2H_5OH at 80 °C.

Table 2 Exploring Generality and Scope of the Novel Reaction[a,b]



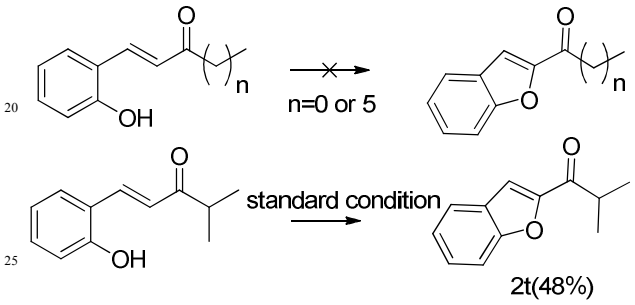
1 **2**



[a]All the reactions were carried out using **1** (0.25 mmol), I_2 (0.025 mmol), TBHP (0.5 mmol) and NaN_3 (0.05 mmol) in C_2H_5OH (4.0 mL) at 80℃. [b]Isolated yields.

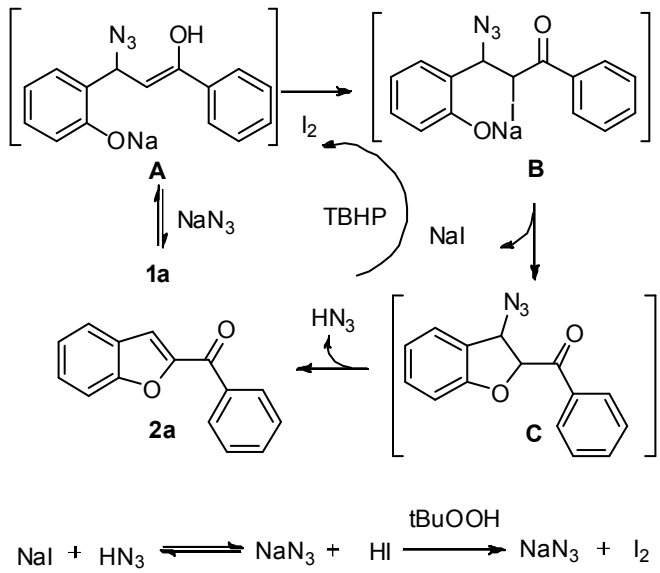
With the optimal reaction conditions in hand, we then examined the transformation of trans-2-hydroxychalcones equipped with a variety of substituents to explore generality and

scope. It was observed that substituents on the R^1 ring almost leaded to good yields (Table 2, **2b**-**2f**, **2h**, **2i**, **2k** and **2l**). O-methyl and p-methyl conducted almost complete transformation (Table 2, **2b** and **2d**). M-methyl, p-methoxyl, m-bromo, o-bromo and o-chloro gave target products in>80% yields (Table 2, **2c**, **2e**, **2h** and **2k**), while p-Br, p-Cl led to the corresponding products in moderate yields (Table 2, **2g** and **2j**). When changing the substituents on R^2 Ring, different results appeared (Table 2, **2m**-**2p**). Substrates equipped with 5-Cl or 5-Br gone through great transformation. Similarly, substrate equipped with methoxyl got middle yield. When R^2 was a strong electron-withdrawing group (5-NO_2), trace desired product was observed under the optimized reaction conditions. Remarkably, this strategy was further successfully applied to heterocyclic substrates to synthesize corresponding products in good yields (Table 2, **2q**-**2s**).



Scheme 2 Further Application of the Novel Reaction

We further applied this practical procedure to the trans-2-hydroxychalcone substituted by alkyl groups (Scheme 3). An interesting result occurred. When alkyl groups linked to the the carbonyl group with primary carbon or secondary carbon, no desired products was isolated. However, trans-2-hydroxychalcone bearing tertiary carbon was successfully transformed to 1-(benzofuran-2-yl)-2-methylpropan-1-one in 48% yield (Scheme 3, **2t**).



Scheme 3 Plausible Mechanism

According to our experimental data, when other additives were employed instead of NaN_3, no desired product was obtained (Table 1, entry 6). Besides, target product was got while catalytic amount of NaN_3 was used (Table 1, entry 14). On the basis of these results, a plausible mechanism was shown in Scheme 4. First, NaN_3 as a nucleophile reacts with **1a** via Michael-type addition reaction to deliver unstable intermediate **A**. This transformation efficiency could be improved in the presence of catalytic amount of iodine. Subsequently, **A** could easily be oxidized by iodine to give intermediate **B**, which is converted to the product **C** after loss of NaI. Then, **C** losses HN_3 catalyzed by I_2, which is similar to loss H_2O. At last, NaI and HN_3 exchanged and oxidized by TBHP to I_2 and NaN_3. Obviously, formation of **2a** was more favorable and fast process.

In summary, this paper described a novel and efficient method for the synthesis of benzofuran derivatives under metal-free conditions. In this transformation, a broad substrate scope has been demonstrated and catalytic amount of NaN_3 plays a crucial role in the oxidative coupling reaction. The possible domino Michael addition and intramolecular oxidative coupling reaction mechanism is also proposed. Studies on novel oxidative functionalization are being actively pursued in this laboratory.

Acknowledgements

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Notes and references

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