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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 and C-heteroatom bond, 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. Numerous methods have been developed for carbon-heteroatom bond formation in last decades. 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.

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. Series of methods for the synthesis of benzofuran derivatives have been reported. 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. However, there are extreme conditions in oxidative coupling reaction with phenolic hydroxyl due to phenols are ready to undergo oxidative dearomatization to yield quinones. 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 revealed that 4-hydroxyacetaminyl aldehydes incorporate into lignins by examining transgenic plants via intermolecular radial coupling reactions (Scheme 1). And authors think that this process appears to reflect simple chemical coupling propensities. Type II, Alessandra Lattanzi and Duan 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, Yoshikai and Zhu 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 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-hydroxylchalcones 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

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<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Additive</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Yield (%)</th>
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<td>83</td>
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</table>

$^{a}$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°C, unless otherwise stated.

$^{b}$Isolated yields.

$^{c}$All TBHP (70% in water).

$^{d}$Other oxidants include PIDA, mCPBA, K$_2$S$_2$O$_8$, DTBP. Other additives include K$_2$CO$_3$, Na$_2$CO$_3$, NaHCO$_3$, NaOH, NaH$_2$PO$_4$·2H$_2$O, KH$_2$PO$_4$, K$_2$PO$_4$·3H$_2$O, KSCN, (NH$_4$)$_2$PO$_4$·3H$_2$O. CH$_3$CN:H$_2$O=1:1. 2.0 equivalent of NaN$_3$ was used. 0.2 equivalent of NaN$_3$ was used. 0.2 equivalent of NaN$_3$ was used. Other acids include p-TSA, BF$_3$·Et$_2$O, TIOH, 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 oxidants: PIDA (iodobenzene diacetate), mCPBA (m-chloroperbenzoic acid), K$_2$S$_2$O$_8$ 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$_2$O, and toluene were also effective 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$_3$·Et$_2$O, p-TSA and TIOH, 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$_2$H$_5$OH at 80°C.

Table 2 Exploring Generality and Scope of the Novel Reaction

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 oxidants: PIDA (iodobenzene diacetate), mCPBA (m-chloroperbenzoic acid), K$_2$S$_2$O$_8$ 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$_2$O, and toluene were also effective 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$_3$·Et$_2$O, p-TSA and TIOH, 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$_2$H$_5$OH at 80°C.

Table 2 Exploring Generality and Scope of the Novel Reaction

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
It was observed that substituents on the R¹ ring almost led to good yields (Table 2, b-2f, 2h, 2i, 2k and 2l). O-methyl and p-methyl conducted almost complete transformation (Table 2, 2b and 2d). M-methyl, p-methoxy, 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 R² Ring, different results appeared (Table 2, 2m, 2n, 2o). Substrates equipped with 5-Cl or 5-Br gone through great transformation. Similarly, substrate equipped with methoxyl got middle yield. When R² was a strong electron-withdrawing group (5-NO₂), 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 benzofuran ring almost led to good yields (Table 2, 2t, 2u and 2v). While p-Br, p-Cl led to the corresponding products in moderate yield. When R² was a strong electron-withdrawing group (5-NO₂), 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, 2w-2y).

According to our experimental data, when other additives were employed instead of NaN₃, no desired product was obtained (Table 1, entry 6). Besides, target product was not obtained when catalytic amount of NaI was used (Table 1, entry 14). On the basis of these results, a plausible mechanism was shown in Scheme 4. First, NaN₃ 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 loses HN₃ catalyzed by I₂, which is similar to loss H₂O. At last, NaI and HN₃ exchanged and oxidized by TBHP to I₂ and Na₂I. 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 NaN₃ 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.

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Notes and references

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