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The Benzoyl Peroxide Promoted Dual C−C Bond Formation via Dual C−H Bond Cleavage: α-Phenanthridinylation of Ether by Isocyanide

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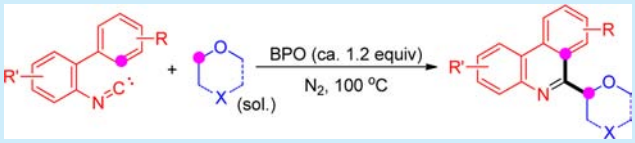
Supporting Information

ABSTRACT: The benzoyl peroxide-promoted α-phenanthridinylation of ether by isocyanide is developed, proceeding through dual C−H bond cleavage and dual C−C bond formation. The procedure tolerates a series of functional groups, such as methyl, fluoro, chloro, acetyl, methoxy carbonyl, cyano, and trifluoromethyl. Thus, it represents a facile pathway leading to 6-substituted phenanthridine derivatives. The addition of radical to the isonitrile followed by a radical aromatic cyclization is involved in this transformation.

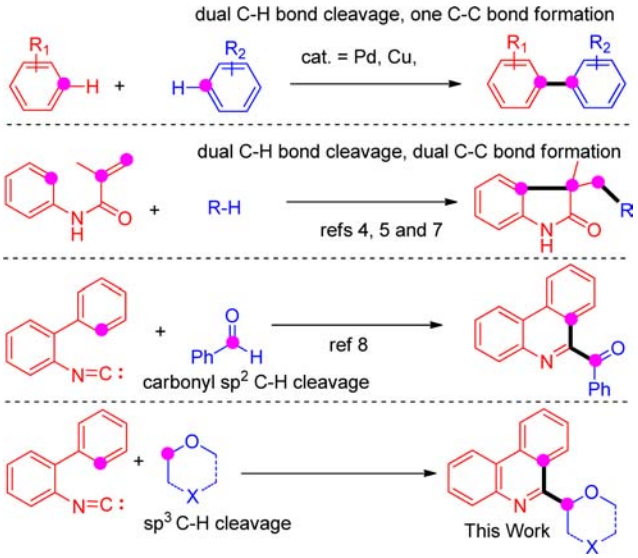


The dual C−H bond functionalization has attracted increasing and continuing interest because it is more sustainable and more atom-economic than the traditional crossing coupling between halides and organometallic reagents. As a result, the oxidative coupling between two reaction partners involving the dual C−H bond cleavage was well developed in the past decade.[1−3] Undoubtedly, the dual C−H bond functionalization along with dual C−C bond formation is beneficial to the diversity and complexity of the final product. In this regard, the difunctionalization of activated alkene through dual C−H bond cleavage was developed by Li,[4] Liu,[5] Zhu,[6] and Duan,[7] respectively (Scheme 1). Similarly, Studer reported a facile pathway leading to 6-benzoyl phenanthridine involving the carbonyl and arene sp^2 C−H bond cleavage (Scheme 1).[8]

Meanwhile, the α-H of the ether is prone to be oxidized to produce a radical in the presence of peroxide.[9] We postulated after the addition of the formed α-radical to isocyanide that cyclization could take place to form the framework of phenanthridine,[10] which is ubiquitous in natural and pharmaceutical compounds (Scheme 1).[11]

With this in mind, we started our study by using the model reaction as follows: 2-phenyl phenyl isocyanide (0.2 mmol), TBHP (70% aqueous, 2.4 mmol) in dioxane (2 mL) under N_2 at 100 °C for 4 h. To our delight, α-phenanthridinylation of ether took place in 15% yield (Table 1, entry 1). Replacing TBHP with DTBP, the yield increased to 40% under 135 °C (Table 1, entry 2). AIBN were totally ineffective for this transformation (Table 1, entry 3). The product was isolated in 18% yield by using aqueous H_2O_2 (Table 1, entry 4). Gratifyingly, the reaction yield was further increased to 74% by employing benzoyl peroxide (BPO). Under O_2 and air, the yield decreased to 42 and 64%, respectively (Table 1, entry 5). In the absence of peroxide, no reaction took place (Table 1, entry 6). The reaction temperature was crucial for this transformation. Under 60 °C, the yield dramatically decreased to 19% (Table 1, entry 7). $FeCl_2$ had no effect on the reaction (Table 1, entry 8). Further study revealed the base decreased or inhibited the reaction (Table 1, entries 9−11).

Scheme 1. Transformations Based on Dual C−H Bond Functionalization



After the establishment of the optimal reaction condition, the scope of isonitrile with substituent on the cyclized phenyl ring was studied, as shown in Figure 1.

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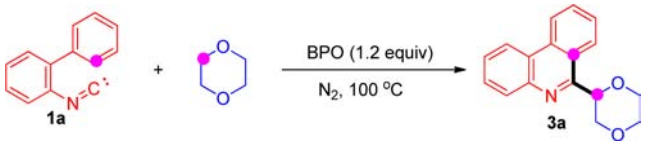
Table 1. Selected Results for Screening the Optimized Reaction Conditions[a]



entry	metal	peroxide	base	temp (°C)	yield (%)[b]
1	–	70% TBHP	–	100	15
2	–	DTBP	–	135	40
3	–	AIBN	–	100	<5
4	–	30% H_2O_2	–	100	18
5	–	BPO	–	100	74 (42)[c] (64)[d]
6	–	–	–	100	0
7	–	BPO	–	60	19
8	$FeCl_2$	BPO	–	100	18
9		BPO	K_2CO_3	100	62
10		BPO	Et_3N	10	<5
11		BPO	Na_2HPO_4	100	54

[a]Reaction conditions: **1a** (0.2 mmol), peroxide (0.24 mmol) (DTBP = di-*tert*-butyl peroxide, BPO = benzoyl peroxide), metal (0.2 equiv), and 1,4-dioxane (2.0 mL) under N_2 for 4 h, sealed tube. [b]Isolated yield. [c]Under O_2. [d]Under air.

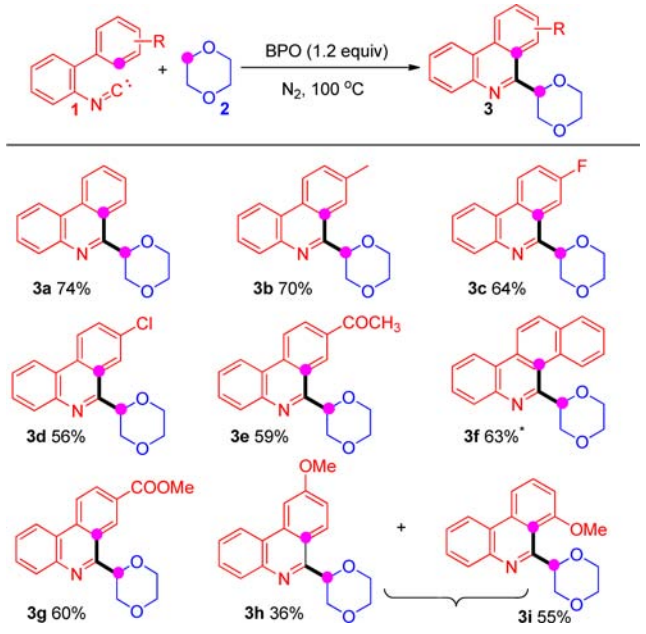


Figure 1. Scope of isonitrile with substituent on the cyclized phenyl ring. Reaction conditions: **1** (0.2 mmol), BPO (ca. 0.24 mmol), 1,4-dioxane (2.0 mL), N_2, 100 °C, 4 h. *BPO (ca. 0.3 mmol).

As expected, all substrates ran smoothly under the standard procedure. Importantly, the reaction was not sensitive to the electronic nature of the substituents on the cyclized phenyl ring, and both electron-withdrawing and -donating substituted substrates worked well to deliver the phenanthridine products in good yields. The procedure tolerated some functional groups, such as methyl, chloro, acetyl and methoxy carbonyl groups, which was suitable for potentially further functionalization. Notably, for the *meta*-substituted substrate, the cyclization preferably took place at the more crowded position (e.g., **3h** and **3i**).

Next, the substrates scope of isonitrile with substitutent on the phenyl ring other than the cyclized phenyl ring was studied, as shown in Figure 2. Once again, the procedure was not

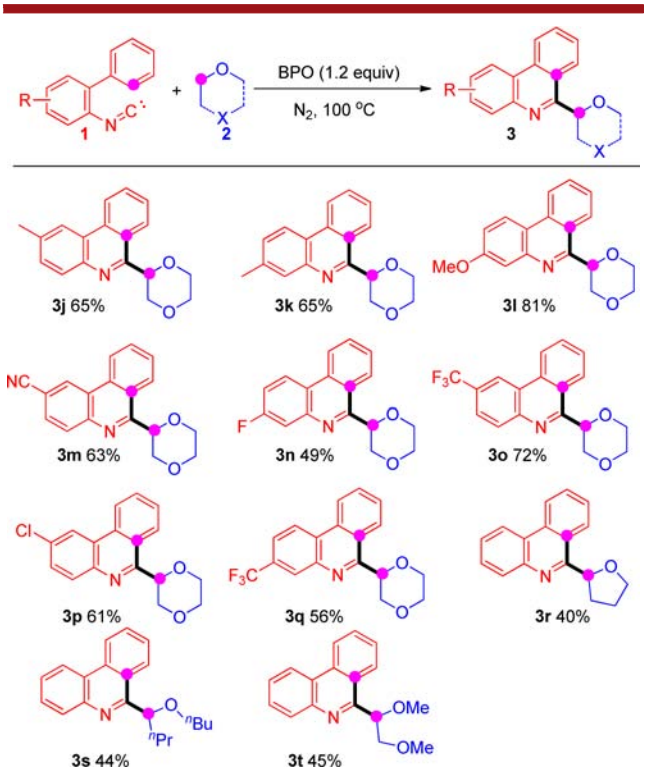


Figure 2. Scope of isonitrile with substituent on the phenyl ring attached with the isocyano group. Reaction conditions: **1** (0.2 mmol), BPO (ca. 0.24 mmol), ether (2.0 mL), N_2, 100 °C, 4 h.

sensitive to the nature of the substituted group, as evidenced by the moderate to good yields of **3j**–**3q**. Chloro, cyano, and trifluoromethyl groups all survived well under the procedure. Notably, THF was a proper reaction partner, providing the phenanthridine analogue **3r** in 40% yield. Importantly, this procedure is not limited to the cyclic ethers. For example, dibutyl ether and dimethoxyethane afforded the desired products **3s** and **3t** in 44 and 45% yields, respectively.

More experiments were conducted to gain some insight into this reaction. First, adding 50 mol % of TEMPO inhibited the reaction (Scheme 2, eq 1). Second, the intermolecular kinetic isotopic experiment confirmed the k_H/k_D for arene C–H bond was 1.0, indicating either electrophilic aromatic substitution or free-radical substitution was involved in the cyclization step (Scheme 2, eq 2).[12] Third, a large kinetic isotope effect was observed for THF under the procedure, indicating the cleavage of sp^3 C–H bond rather than the sp^2 C–H bond was involved as the rate-determining step for this transformation (Scheme 2, eq 3). Furthermore, the competitive experiment revealed the electron-withdrawing group was beneficial for this transformation, which was consistent with a radical cyclization pathway (Scheme 2, eq 4).

On the basis of these experimental results, a proposed mechanism is illustrated in Scheme 3. First, the homolytic cleavage of BPO produces benzoyloxy radical, which abstracts the α-H of dioxane to form a radical species **4**. Then, the addition of radical species **4** to isonitrile produces another radical intermediate **5**. Subsequently, the intramolecular radical cyclization of intermediate **5** takes place to form the radical

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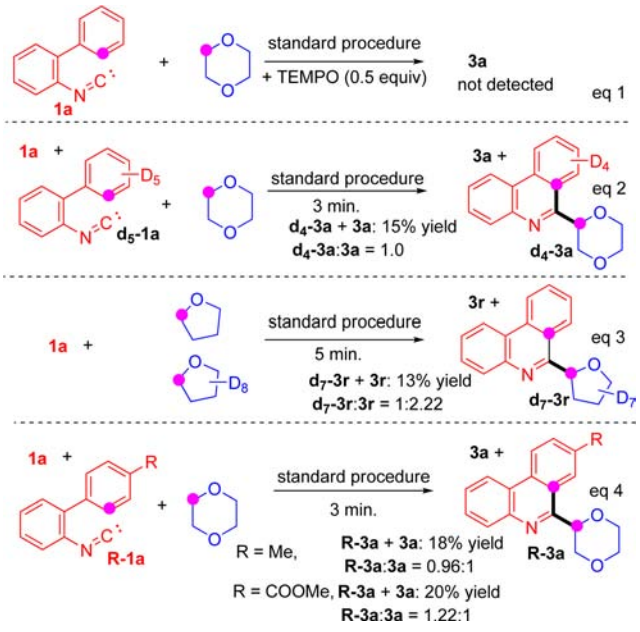
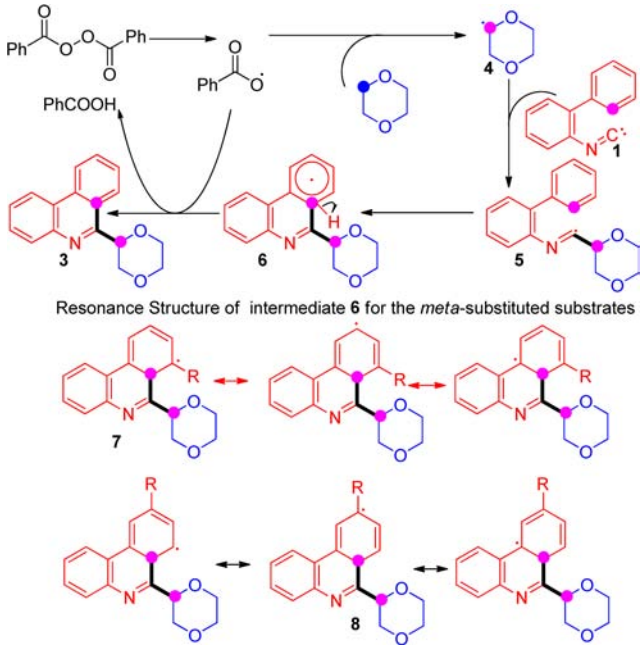
Scheme 2. Preliminary Mechanism Study



Scheme 3. Proposed Mechanism



intermediate **6**. Finally, phenanthridine is formed by the assistance of benzoyloxy radical, along with 1 equiv of benzoic acid. In the case of substrate with *meta*-substitutent on the cyclized phenyl ring, the cyclization at the crowded position is preferred because the resonance structure **7** is more stable than that of **8**.[13]

In conclusion, we have developed a BPO-promoted α-phenanthridinylation of ether by isocyanide.[14] This procedure involved dual C−C bond formation via dual C−H bonds cleavage. This work represents a facile and straightforward pathway leading to 6-alkyl phenanthridine.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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