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The benzoyl peroxide-promoted functionalization of simple alkanes with 2-aryl phenyl isonitrile†

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The benzoyl peroxide (BPO)-promoted phenanthridinylation of simple alkanes with isonitrile is developed *via* C(sp^3)–H and C(sp^2)–H bond cleavage. This procedure is featured by dual C–C bond formation proceeding with the addition of an alkyl radical to isonitrile followed by radical aromatic cyclization.

The direct and selective functionalization of the sp^3 C–H bond constitutes a long standing goal in synthetic organic chemistry because of its high bond-dissociation energy (BDE) and low polarity. As a result, the chelating group assisted sp^3 C–H bond functionalization and the activation of the sp^3 C–H bond, which was benzylic or adjacent to the oxygen or nitrogen atom, have been well developed in the past few years.[1] The functionalization of simple alkanes remains more practicable because they are major constituents of petroleum and natural gas.[2] In 2008, Li reported the Ru-catalyzed oxidative coupling of 2-aryl pyridine with cycloalkanes.[3] Bettinger, Ochiai and Hartwig described the conversion of inactive alkane to amine and amide, respectively.[4] Recently, Antonchick developed the direct oxidative cross-coupling of alkanes with heteroarenes and (thio)chromones.[5] Fokin reported a highly efficient enantioselective C–H insertion of azavinyl carbenes into inactive alkanes.[6]

The C–H bond of alkanes is prone to be functionalized *via* a radical pathway under certain reaction conditions.[7] Very recently, Wei reported the copper-catalyzed alkenylation of alkanes.[8] Meanwhile, the cascade radical functionalization of the inactive C–H bond attracted much attention.[9] Liu developed free-radical cascade alkylarylation of alkenes with simple alkanes leading to oxindoles.[10] However, the functionalization of simple alkanes toward diversity and complexity of a target organic compound is a highly desired goal for organic chemists.

The unique property of isonitrile inspired us to test the reaction of isonitrile with simple alkanes, proceeding through a radical pathway. Herein, we wish to report our study on the sequential addition of alkyl radical/intramolecular cyclization of isonitrile. Such a similar strategy has been developed for the synthesis of 6-substituted phenanthridine,[11] which is widely found in natural and pharmaceutical compounds.[12] Compared with Yu's procedure,[13] it involves (1) transition-metal free reaction conditions; (2) the employment of a simple alkane rather than an alkyl bromide.

The first glimpse of success was obtained by using the reaction of 2-phenyl phenyl isonitrile and cyclohexane with the combination of $FeCl_2$ and TBHP as the model reaction at 100 °C, which provided 6-cyclohexanyl phenanthridine in 28% yield (Table 1, entry 1). Replacing TBHP with other oxidants, such as

Table 1 Selected results for optimal reaction conditions[a]

Entry	Metal	Peroxide	*T*/°C	Yield[b] (%)
1	$FeCl_2$	TBHP	100	28
2	$FeCl_2$	H_2O_2	100	<1
3	$FeCl_2$	DTBP	100	<5
4	$FeCl_2$	$K_2S_2O_8$	100	<1
5	$FeCl_2$	BPO	100	67
6	$CuCl_2$	BPO	100	25
7	CuI	BPO	100	<1
8	—	BPO	100	75(76)[c]
9	—	BPO	80	69
10	—	BPO	120	74
11	—	—	100	<1

[a] Reaction conditions: **1a** (0.2 mmol), peroxide (2.2 equiv.) (DTBP = di-*tert*-butyl peroxide, TBHP = *tert*-butyl hydroperoxide, BPO = benzoyl peroxide), and cyclohexane (2.0 mL) under air for 4 h, sealed tube. [b] Isolated yield. [c] N_2.

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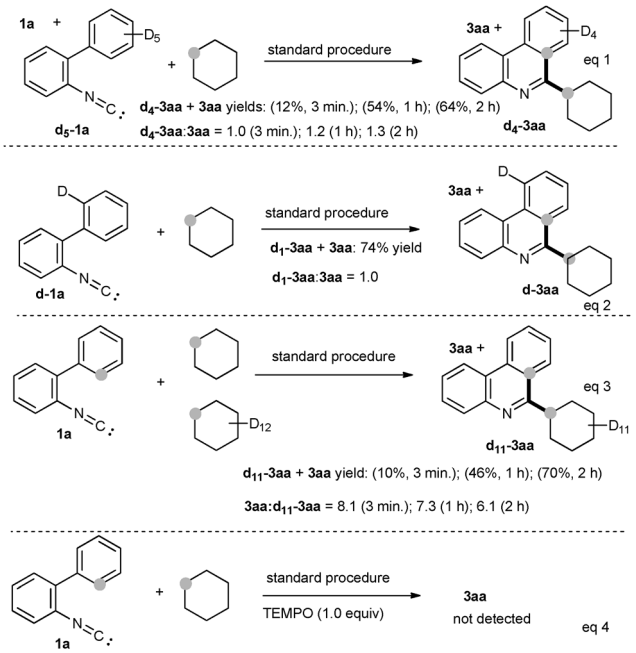
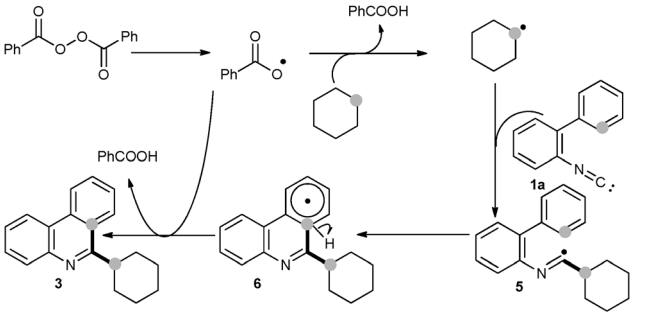


Scheme 1 Preliminary mechanistic study.

DTBP, H_2O_2, and $K_2S_2O_8$, resulted in no reaction (Table 1, entries 2–4). To our delight, the yield dramatically increased to 67% by using BPO (Table 1, entry 5).[14] $CuCl_2$ and CuI were found to be less effective or ineffective for this transformation (Table 1, entries 6 and 7). The blank experiment confirmed that $FeCl_2$ was not essential for this transformation (Table 1, entry 8). Although O_2 may inhibit the radical reaction, the yield did not increase under N_2 (Table 1, entry 8). The yield slightly decreased at 80 °C and a comparable yield was obtained at 120 °C (Table 1, entries 9 and 10). A further study revealed that no reaction took place in the absence of BPO (Table 1, entry 11).

More experiments were conducted to gain some insight into the reaction. Firstly, the inter- and intra-molecular kinetic isotope effects of the arene C–H bond were tested and the K_H/K_D was found to be nearly 1.0 and 1.0, respectively (eqn (1) and (2), Scheme 1). These results implied that (1) the cleavage of the arene C–H bond was not the rate-determining step; (2) either the radical or electrophilic aromatic substitution pathway was involved in this transformation.[15] However, a large kinetic isotope effect (K_H/K_D = 6.1–8.1) was detected for the sp^3 C–H bond in cyclohexane, which confirmed the slow cleavage of the sp^3 C–H bond (eqn (3), Scheme 1). Finally, 1.0 equivalent of TEMPO was added and the reaction was inhibited, which strongly supported the radical pathway (eqn (4), Scheme 1).

Based on these experimental results, the proposed mechanism is outlined in Scheme 2. Initially, the benzoyl radical is formed by the homolytic cleavage of BPO. Then the formed benzoyl radical abstracts one H of cyclohexane to form a cyclohexanyl radical. This step is the rate-determining step as confirmed by the KIE. Next, the addition of the cyclohexanyl radical to isonitrile produces another radical intermediate **5**. Subsequently, the intramolecular radical cyclization of intermediate **5** takes place to form radical intermediate **6**. Finally, the benzoyl radical abstracts one H from intermediate **6** to form phenanthridine.



Scheme 2 Proposed mechanism.

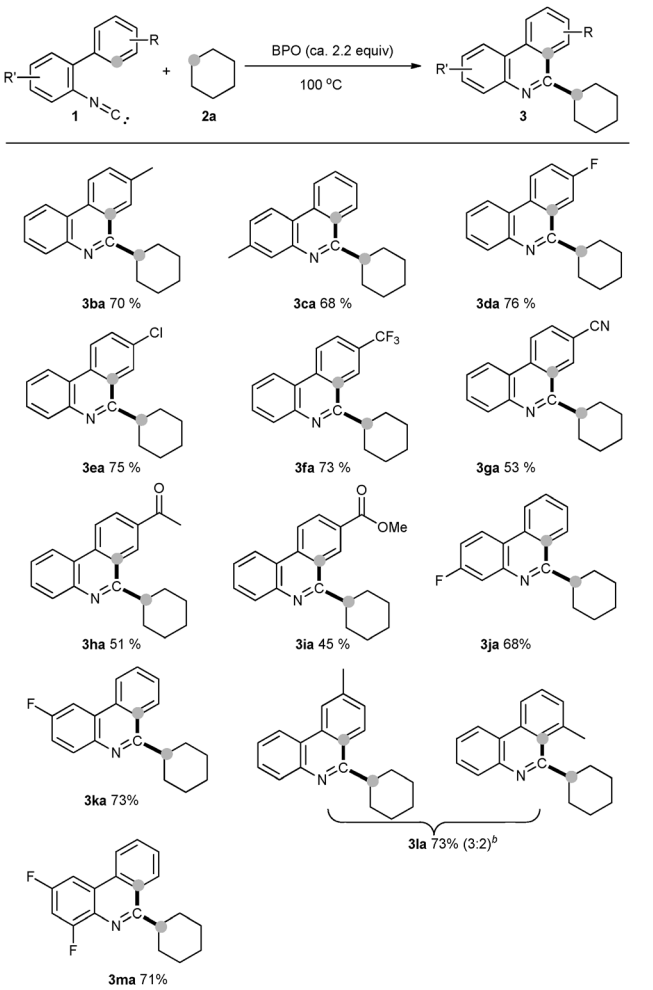


Fig. 1 Substrate scope of isonitrile. [a] Reaction conditions: **1** (0.2 mmol), BPO (*ca.* 0.44 mmol), cyclohexane (2.0 mL), 100 °C, 4 h. [b] Determined by ^{1}H NMR spectroscopy.

The substrate scope of isonitrile was studied, as shown in Fig. 1. As expected, all substrates smoothly underwent the reaction. This procedure tolerated some functional groups, such as fluoro, chloro, trifluoromethyl, acetyl, cyano and methoxycarbonyl, which were applicable to further potential functionalization. Since a radical cyclization pathway was involved in this transformation, as expected, the reaction efficiency was not

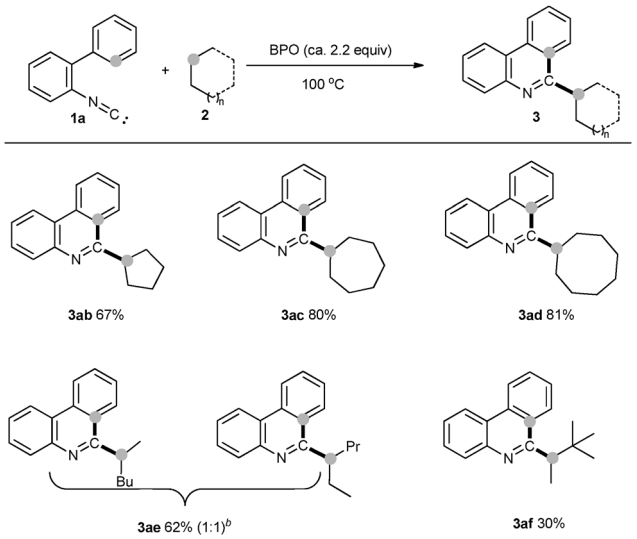


Fig. 2 Substrate scope of alkanes. [a] Reaction conditions: **1** (0.2 mmol), BPO (*ca.* 0.44 mmol), alkanes (2.0 mL), 100 °C, 4 h. [b] Determined by ^{1}H NMR spectroscopy.

decreased by the electron-withdrawing groups attached in the cyclized phenyl ring. For example, **3da**, **3ea** and **3fa** were all isolated in good yield. However, moderate yields were obtained for **3ga**, **3ha** and **3ia**, which may be at least partly due to potential side reaction derived from the substituted groups. For the isonitrile possessing a *meta*-methyl on the cyclized phenyl ring, **3la** was isolated in 73% yield with 3 : 2 selectivity, where the less hindered isomer was the main product.

Next, the substrate scope of alkanes was studied, as shown in Fig. 2. Once again, cyclopentane, cycloheptane and cyclooctane worked well, providing the desired products **3ab**, **3ac**, **3ad** and **3af** in 67%, 80%, 81% and 30% yields, respectively. Particularly, hexane took part in the reaction, leading to the 2- and 3- functionalized products **3ae** (1 : 1) in total 62% yield.

In conclusion, we have developed the BPO-promoted phenanthridinylation of simple alkanes with isonitrile.[16] The procedure involves dual C–C bond formation *via* dual C–H bond cleavage. The cleavage of the sp^3 C-H bond is the rate-determining step in this transformation.

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