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Metal-free radical oxidative decarboxylation/cyclization of acylperoxides and 2-isocyanobiphenyls

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A metal-free radical oxidative decarboxylation/cyclization of acylperoxides and 2-isocyanobiphenyls was achieved, leading to 6-arylphenanthridines as well as 6-alkylphenanthridines in moderate to good yields. The procedure was featured with 10 simple condition, metal-free and base free. It represents a practical approach to access 6-aryl/alkyl phenanthridines.

The oxidative coupling methodology involving C-H functionalization has established as a powerful and efficient strategy for organic synthesis due to the avoidance of pre-¹⁵ functionalization process.¹ The radical-driven oxidative coupling has lately emerged as a promising approach in this area.² Most recently, radical oxidative cyclization of 2-isocyanobiphenyls with different radical precursors to provide 6-substituted phenanthridines which are widely present in natural, ²⁰ pharmaceutical and bioactive compounds³ has been developed. For example, Chatani reported the first oxidative cyclization of 2isocyanobiphenyls by aryl/alkyl boronic acid as radical precursors to synthesize 6-aryl/alkyl phenanthridines (Scheme 1, eq. 1).⁴ Subsequently, we ⁵ and other groups⁶ developed the 25 radical isonitrile insertion reaction with various radical precursors toward a series of 6-substituted phenanthridines. However, more environmentally friendly method such as metal-free and base-free for such transformation is still highly desired.

- Metal-catalyzed decarboxylative arylations started from ³⁰ carboxylic acids has been established as a powerful tool for carbon–carbon or carbon–heteroatom bonds formation.⁷ However, in most cases, noble metals were always required with high reaction temperatures. Aryl radicals could generate from the decarboxylation of arylcarboxyl radicals that produced from
- ³⁵ homolytic O-O bond cleavage of aryl acylperoxides under mild condition.⁸ In 2009, Yu demonstrated the first Pd-catalzyed decarboxylative *ortho*-arylation of 2-phenylpyridines with benzoyl peroxides via radical pathway (Scheme 1, eq. 2).⁹ Inspired by these works, we envision that intermolecular addition
- ⁴⁰ of aryl radicals that derived from thermal decomposition of aryl acylperoxides to isonitrile of 2-arylphenylisonitrile to produce the imidoyl radical, followed by intramolecular aromatic homolytic substitution, could lead to 6-aryl phenanthridines. Herein, aryl acylperoxides are demonstrated as a good aryl radical precursor
- ⁴⁵ to react smoothly with 2-isocyanobiaryls to access 6-aryl phenanthridines without the assistance of transition metal or base (Scheme 1, eq. 3).

Scheme 1. Transformations based on aryl radical



Table 1. Screening the optimal conditions



Reaction conditions: 1a (0.2 mmol), 2a (0.6 mmol) and solvent (2 mL), 100 °C, 10 h, N₂.

Initially, the reaction of 2-isocyanobiphenyl (1a) with benzoyl peroxide (2a) in CH₃CN was investigated. To our delight, the desired product **3aa** was obtained in 32% yield (Table 1, entry 1). Next, other solvents were screened. Among the solvents screened, 60 PhCF₃ performed best efficiency, providing 80% yield of the

product (Table 1, entry 6). The reaction did not provide any product in DMSO (Table 1, entry 7).

After the establishment of the optimal reaction condition, a series of 2-isocyanobiaryl compounds were explored. As shown

- s in Figure 1, various functional groups such as fluoro, chloro, trifluoromethyl and trifluoromethoxy groups were tolerated well affording the products in good yields. The reaction was not significantly affected by the substituent on the aromatic ring attached to isocyanides, such as methyl, fluoro, chloro,
- ¹⁰ trifluoromethyl groups, leading to the 6-arylphenanthridines **3ba-3ga** in good yields. Subsequently, the effect of substituents on 4-position of the aromatic ring were surveyed. The isocyanides **1h-1i** bearing electron-donating groups gave the product in higher yields than those of electron-withdrawing analogues **1j-1k**. 2-
- ¹⁵ Isocyanobiphenyl bearing *ortho* substituent performed lower reactivity due to the steric effect (Figure 1, **3la**). To investigate the regioselectivity of the cyclization, the 2-isocyanobiphenyl bearing a *meta*-methyl (**1o**) was investigated resulting with a mixture of two regioisomers in a ratio of 1:2 (Table 2, **3oa+3oa'**). ²⁰ Notably, halogen groups were tolerable, which was suitable for
 - potential further functionalization.





^{*a*} Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol) and PhCF₃ (2 mL), N₂, 25 100 °C, 10 h. ^{*b*} the ratio was determined by ¹H NMR.

Journal Name, [year], [vol], 00-00

Next, various aryl acylperoxides were examined for this transformation. As shown in Figure 2, various functional groups such as methoxy, trifluoromethyl, fluoro Dehloro and Active Complete Strates and para-substituted aryl acylperoxides all worked well in the present system to afford the 6-arylphenanthridines in good yields (Figure 2, **3ab-3aj**). To further explore the scope of the reaction, alkyl acylperoxides such as decanoic peroxyanhydride ²⁵ (**2k**), lauroyl peroxide (**2l**), stearic peroxyanhydride (**2m**) and 2-ethylhexanoic peroxyanhydride (**2n**) were subjected to the precedure. Delightedly, 6-alkylphenanthridines were provided

Figure 2. Scope of acylperoxides

with good yields (Figure 2, 3ak-3an).



Reaction conditions: 1a (0.2 mmol), 2 (0.6 mmol) and PhCF₃ (2 mL), N₂, 100 $^{\circ}$ C, 10 h.

When 3.0 equiv of 2,2,6,6-tetramethylpiperidine oxide 45 (TEMPO) was added as a radical inhibitor, the desired product was not observed, providing evidence for the free radical mechanism. Based on the experimental result, a possible mechanism is illustrated in Scheme 2. Initially, the thermal decomposition of benzoyl peroxide (**2a**) along with release of 50 CO₂ produces the phenyl radical **A**.⁸ Then, the addition of radical **A** to isonitrile of 2-isocyanobiaryl **1a** forms the imidoyl radical **B**, which upon intramolecular cyclization gives radical intermediate **C**. Finally, hydrogen abstraction of radical intermediate **C** takes place to provide the product **3aa**.

2 |

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In conlusion, we have developed a metal-free radical oxidative decarboxylation/cyclization of acylperoxides and 2isocyanobiphenyls. Through this radical oxidative decarboxylation/cyclization pathway under metal-free and 10 base free condition, 6-arylphenanthridines as well as 6alkylphenanthridines ware obtained in moderate to good

alkylphenanthridines were obtained in moderate to good yields. It represents a practical approach to access 6substituted phenanthridines.

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Journal Name, [year], [vol], 00-00 | 3

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