

# One-Pot Synthesis of N-( $\alpha$ -Peroxy)Indole/Carbazole via Chemoselective Three-Component Condensation Reaction in Open Atmosphere

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**Supporting Information** 

**ABSTRACT:** A facile one-pot synthesis of N-( $\alpha$ -peroxy)indole and N-( $\alpha$ -peroxy)carbazole has been developed using metal-free, organo-acid-catalyzed three-component condensation reactions of indole/carbazole, aldehyde, and peroxide. Based on the reaction discovered, a new synthetic proposal for



Fumitremorgin A and Verruculogen is introduced. Such a protocol could be easily handled and scaled up in an open atmosphere with a wide substrate scope, enabling the construction of a new molecule library.

Many indole-, carbazole-, and peroxide-containing compounds possess antimalarial, antibacterial, and antitumor activities.<sup>1</sup> For example, the indoloquinoline alkaloid, cryptolepine, has been used as an antimalarial drug especially in central and western Africa and also as an anticancer drug to intercalate into DNA at cytosine–cytosine sites.<sup>2</sup> Artemisinin (qinghaosu), a peroxide-containing natural product, has long been used as a highly effective antimalarial drug.<sup>3</sup> As parasites evolve to be more resistant to existing drugs, continuous design and synthesis of new antimalarial compounds are desirable.<sup>4</sup>

The  $\alpha$ -amino peroxide pharmacophore is one of the salient structural features that has been found to be effective in antimalarial activities.<sup>5</sup> Landmark accomplishments have been achieved for the synthesis of  $\alpha$ -amino peroxides, such as metal/ iodine/Brønsted acid-catalyzed benzylic N-adjacent C-H peroxidation,<sup>6</sup> radical oxidation of amino acid derivatives under 350 nm light irradiation,<sup>7</sup> peroxide nucleophilic addition to imines,<sup>5,8</sup> and FeCl<sub>3</sub>-catalyzed condensation of carbonyl, <sup>t</sup>BuOOH, and TMS-azide.<sup>9</sup> These methods provided tools to synthesize  $\alpha$ -N-peroxy compounds, some of which have been found to possess in vitro antimalarial activities.<sup>5</sup> Unfortunately, all of these protocols require either a special substrate (e.g., benzylic amine with N protected) or special conditions (e.g., heavy metal or  $h\nu$ ). Moreover, none of them can be integrated with the readily oxidizable indole residue and the classic oxidant of peroxide to give N-( $\alpha$ -peroxy)indole, a somewhat rare structure that is present in active natural products. For example, Fumitremorgin A,<sup>10</sup> Verruculogen,<sup>11</sup> and its acetoxy derivative<sup>1</sup> (Figure 1), three of the top-end products of the Fumitremorgin family, contain an astounding  $\alpha$ -indole amino endoperoxide bridge. It was found that Fumitremorgin A affects the brain <sup>3</sup> while Verruculogen decreases the GABA level and stem, inhibits the mammalian cell cycles.<sup>1c</sup> A non-heme Fe(II)catalyzed oxygen insertion pathway was proposed biosyntheti-



**Figure 1.** Literature-reported and our proposal for the late-stage peroxide bridge formation and the key N-( $\alpha$ -peroxy)indole motif (in the dashed box).

cally,<sup>14</sup> while no practical applicable method has been developed over 40 years since its discovery. We have proposed a nucleophilic annulation strategy to construct the  $\alpha$ -indole peroxide bridge (Figure 1) through an intermolecular threecomponent condensation reaction of indole, aldehyde, and peroxide.<sup>15</sup> Baran et al.<sup>16</sup> have used a similar strategy in their recent total synthesis of Verruculogen and Fumitremorgin A.

Received: October 5, 2015

Herein, we present our study of this condensation reaction to build a new molecule library for new drug discoveries.

Indole derivative C, 3-methylbutanal, and <sup>t</sup>BuOOH were chosen first as the model substrates to screen the reaction conditions. As demonstrated in Table 1, *p*-toluenesulfonic acid

#### Table 1. Reaction Condition Screening<sup>a</sup>



<sup>*a*</sup>Reaction conditions: C (0.1 mmol), aldehyde (0.2 mmol), and <sup>*b*</sup>BuOOH (0.6 mmol) in 2 mL of solvent, rt, air. Then PTSA (ca. 3 mg) was added. <sup>*b*</sup>Yield determined by <sup>*b*</sup>H NMR data of reaction mixture. <sup>*c*</sup>The dr value was found to be 1:1 in all cases. <sup>*d*</sup>Acetic acid (0.1 mmol) was used instead of PTSA. <sup>*e*</sup>Isolated yield. <sup>*fi*</sup>BuOOH was used as 75% solution in water. <sup>*g*</sup>H<sub>2</sub>O<sub>2</sub> (30% solution in water) was used instead of <sup>*t*</sup>BuOOH.

(PTSA), a readily available organic acid, catalyzed the reaction with a much higher efficiency than other acids, such as acetic acid (entry 1, Table 1). Solvent or reagents with a large amount of water may generate a lot of byproducts (entries 3 and 4), but exposure to moisture is tolerated. This reaction can thus be performed in open air, and the PTSA can be used without further dehydration treatment. The choice of solvent was found to be crucial for the condensation. No product was obtained when high polar solvents, such like acetone, DMF, and DMSO, were used as the reaction medium. When acetonitrile, ethyl acetate, and ethanol were applied as the reaction solvent, the reaction only gave the desired product in relatively low yields. Nonpolar solvents such as toluene were not good for the reaction, presumably due to poor solubility. To our delight, chlorinated solvents, such as DCM, DCE, and CHCl<sub>3</sub>, could significantly improve both the reaction rate and the product yield (entries 2, 5, and 6). With DCM as the solvent, the solution color changed immediately after the addition of a catalytic amount of PTSA into the mixture of aldehyde, indole, and peroxide, at which point the TLC and in situ NMR analysis showed a complete conversion and high yield of the desired N-( $\alpha$ -peroxy)indole product (entry 2).

A wide substrate scope with good functional group tolerance and easy scalability are important characteristics for practical applications (e.g., building a library and high-throughput biological screening). The metal-free condition is also highly desired, especially in the pharmaceutical industry. Encouraged by the mild reaction conditions described above, we then examined the general applicability of this method to build a small-molecule library by changing the condensation partners, as summarized in Scheme 1. All condensation of indoles, aldehydes, and peroxides with various substituents and complexity were tolerated, and the





<sup>*a*</sup>Reaction conditions: indole (1 mmol), aldehyde (2 mmol), peroxide (6 mmol for <sup>*t*</sup>BuOOH and 4 mmol for the others), PTSA (0.1 mmol, 10 mol %) in CH<sub>2</sub>Cl<sub>2</sub>, at rt, air. Isolated yield. <sup>*b*</sup>The reaction was carried out for 2 h.

corresponding N-( $\alpha$ -peroxy)indole compounds were prepared in good to excellent yields. Moreover, indoles with or without the electron-donating substituent of a methoxy group on the aryl ring gave no apparent difference in activity, and no oxidized product of the readily oxidizable methoxyindole was observed. Substituents on the side chain of indole with various functional groups are well-compatible with the reaction conditions. The structure of the peroxide counterpart can also be easily extended (1e-1i, Scheme 1), providing more diversities to the molecular library, which demonstrated the broad substrate scope of this method. It is noteworthy that the pentacyclic indole derivative with the core structure of Verruculogen and Fumitremorgin A can produce the desired peroxide product with 75% yield (1j, Scheme 1), indicating the possibility of using this protocol in natural product synthesis. C-3 unsubstituted indole produced other products instead of the desired *N*-( $\alpha$ -peroxy)indole under the standard conditions (see details in Supporting Information). Similar results were observed in the  $\alpha$ -azide peroxide construction reaction,<sup>9</sup> where aromatic aldehydes with electron-withdrawing substituents gave acceptable reactivity and yield of the desired product (1k, Scheme 1). However, arene with a strong electron-donating substituent resulted in compromised reactivity and yield of the desired product (1l, Scheme 1), presumably due to the competition of the Baeyer–Villiger rearrangement.<sup>9</sup>

To understand the reaction mechanism of the condensation process, we performed control experiments, as shown in Scheme 2. The formation of peroxide hemiacetal **2a** and acetal **2d** was

Scheme 2. Control Experiments<sup>*a,b*</sup>



<sup>*a*</sup>Reaction performed in air. <sup>*b*</sup>Yields based on <sup>1</sup>H NMR of the crude reaction mixture.

observed immediately after the addition of PTSA to the mixture of aldehyde and peroxide in DCM, both of which were found to be reactive with indole to give the *N*-( $\alpha$ -peroxy)indole. On the other hand, although nucleophilic addition of indole to aldehyde has been reported,<sup>17</sup> no reaction was observed in the abovementioned conditions. Meanwhile, di-*tert*-butyl peroxide and *tert*-butyl peroxybenzoate, without a free nucleophilic hydroperoxide group, were found to be unreactive. These observations clearly indicate that a peroxycarbenium ion intermediate is involved in the reaction mechanism, similar to that proposed by Pramanik and Ghorai for the formation of the  $\alpha$ -azide peroxide (Scheme 3).<sup>9</sup> Nucleophilic addition of indole to the peroxycarbenium ion then produces the *N*-( $\alpha$ -peroxy)indole.

Since the first report on the isolation and antibiotic properties of murrayanine from *Murraya koenigii Spreng* by Chakraborty et al., carbazole alkaloids have attracted significant interest from chemists and biologists due to their intriguing structural features and promising biological activities.<sup>18</sup> Although a naturally occurring carbazole peroxide compound has not been discov-





ered, the intriguing importance of both peroxide and carbazole, as well as the already established indole peroxide alkaloids of Fumitremorgin A and Verruculogen, prompted us to further extend the protocol to combine the two moieties of carbazole and peroxide in one N-( $\alpha$ -peroxy)carbazole molecule. On the other hand, while the N-( $\alpha$ -alkoxyalkyl)amines, including N-( $\alpha$ -alkoxyalkyl)carbazoles, have been synthesized and found to have good bactericidal and fungicidal activity, <sup>19</sup> to our best knowledge, the N-( $\alpha$ -peroxy)carbazole has not been mentioned yet. As shown in Scheme 4, the condensation processed smoothly under





"Reaction conditions: carbazole (1 equiv), aldehyde (2 equiv), peroxide (5.5 M in decane, 6 equiv), PTSA (0.1 mmol, 10 mol %) in  $CH_2Cl_2$ , at rt, air. Isolated yield.

standard conditions, and the desired N-( $\alpha$ -peroxy)carbazoles were obtained in excellent yields within a few minutes. Notably, all of these reactions were performed in an open flask without any inert gas protection, and the pure 'BuOOH was replaceable with safer 'BuOOH solution in decane, favorable for future scale-up of the synthetic process. The N-( $\alpha$ -tert-butylperoxy)heptyl carbazole structure (**4c**, Scheme 4) was further evidenced by crystal X-ray analysis (Supporting Information). Other nitrogen hetero-compounds, such as diphenylamine, 10,11-dihydro-5H-dibenzo-[b,f]azepine, 1H-benzo[d]-imidazole, and 1H-benzo[d]-imidazole, were found to be unreactive under the standard conditions.

In conclusion, a facile chemoselective methodology for the synthesis of N-( $\alpha$ -peroxy)indole and N-( $\alpha$ -peroxy)carbazole has been developed via a one-pot, rapid, three-component reaction of indole/carbazole, aldehyde, and peroxide using a simple organic acid (PTSA) as the catalyst, without any inert gas protection. This approach provides direct access to a new class of  $\alpha$ -amino peroxides and could be easily scaled up. Additional investigation into the enantioselective synthesis and diversity-oriented synthesis of a molecular library, with the aim of developing new antimalarial drugs (novel molecules merging indole/carbazole and peroxide), is under active consideration, and the results will be reported in due course.

Caution! Anhydrous or highly concentrated solutions of TBHP are potentially hazardous and can undergo violent decomposition upon exposure to certain metal salts. Reactions and subsequent operations involving peroxides should be run behind a safety shield. All hazardous materials should be handled in accordance with the standard procedure described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, DC. 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog. php?record\_id=12654).

# ASSOCIATED CONTENT

## Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02881.

Experimental procedures, characterization data, and NMR spectra (PDF) X-ray crystallographic data for **4c** (CIF)

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#### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

Financial support was provided by the Graduate fellowship of Peking University Shenzhen Graduate School and KAUST baseline fund BAS/1/1375.

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