One-Pot Synthesis of *N*-(α -Peroxy)Indole/Carbazole via Chemoselective Three-Component Condensation Reaction in Open Atmosphere

Xinbo Wang,^{*,†,‡} Yupeng Pan,[†] Kuo-Wei Huang,[†] and Zhiping Lai^{*,†}

[†]Division of Physical Science and Engineering, King Abdullah University of Science and Technology (KAUST), Thuwal, 23955-6900, Kingdom of Saudi Arabia

[‡]Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen 518055, China

S Supporting Information

ABSTRACT: A facile one-pot synthesis of *N*-(α -peroxy)-indole and *N*-(α -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 Fumitremogin 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.

- Mild reaction conditions
- Metal-free
- Wide substrate scope
- Rapid and scalable
- Open atmosphere

Many indole-, carbazole-, and peroxide-containing compounds possess antimalarial, antibacterial, and antitumor activities.¹ 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.² Artemisinin (qinghaosu), a peroxide-containing natural product, has long been used as a highly effective antimalarial drug.³ As parasites evolve to be more resistant to existing drugs, continuous design and synthesis of new antimalarial compounds are desirable.⁴

The α -amino peroxide pharmacophore is one of the salient structural features that has been found to be effective in antimalarial activities.⁵ Landmark accomplishments have been achieved for the synthesis of α -amino peroxides, such as metal/iodine/Brønsted acid-catalyzed benzylic *N*-adjacent C–H peroxidation,⁶ radical oxidation of amino acid derivatives under 350 nm light irradiation,⁷ peroxide nucleophilic addition to imines,^{5,8} and FeCl₃-catalyzed condensation of carbonyl, ^tBuOOH, and TMS-azide.⁹ These methods provided tools to synthesize α -*N*-peroxy compounds, some of which have been found to possess in vitro antimalarial activities.⁵ 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* ν). Moreover, none of them can be integrated with the readily oxidizable indole residue and the classic oxidant of peroxide to give *N*-(α -peroxy)indole, a somewhat rare structure that is present in active natural products. For example, Fumitremogin A,¹⁰ Verruculogen,¹¹ and its acetoxy derivative¹² (Figure 1), three of the top-end products of the Fumitremogin family, contain an astounding α -indole amino endoperoxide bridge. It was found that Fumitremogin A affects the brain stem,¹³ while Verruculogen decreases the GABA level and inhibits the mammalian cell cycles.^{1c} 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*-(α -peroxy)indole motif (in the dashed box).

cally,¹⁴ while no practical applicable method has been developed over 40 years since its discovery. We have proposed a nucleophilic annulation strategy to construct the α -indole peroxide bridge (Figure 1) through an intermolecular three-component condensation reaction of indole, aldehyde, and peroxide.¹⁵ Baran et al.¹⁶ have used a similar strategy in their recent total synthesis of Verruculogen and Fumitremogin A.¹⁷

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 ^tBuOOH 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^a

entry	solvent	time	yield (%) ^{b,c}	entry	solvent	time	yield (%) ^{b,c}
1 ^d	DCM	1 h	20	8	DMF	1 h	NR
2	DCM	5 s	85 (84 ^e)	9	THF	1 h	NR
3 ^f	DCM	5 s	complex	10	DMSO	1 h	NR
4 ^g	DCM	0.5 h	complex	11	MeCN	0.5 h	40
5	DCE	5 s	84	12	EA	1 h	17
6	CHCl ₃	5 s	86	13	toluene	1 h	NR
7	acetone	1 h	NR	14	EtOH	0.5 h	35

^aReaction conditions: **C** (0.1 mmol), aldehyde (0.2 mmol), and ^tBuOOH (0.6 mmol) in 2 mL of solvent, rt, air. Then PTSA (ca. 3 mg) was added. ^bYield determined by ¹H NMR data of reaction mixture. ^cThe dr value was found to be 1:1 in all cases. ^dAcetic acid (0.1 mmol) was used instead of PTSA. ^eIsolated yield. ^f^tBuOOH was used as 75% solution in water. ^gH₂O₂ (30% solution in water) was used instead of ^tBuOOH.

(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 CHCl₃, 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*-(α -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

Scheme 1. Synthesis of *N*-(α -Peroxy)indole from the Three-Component Condensation Reaction of Various Indoles, Aldehydes, and Peroxides^a

^aReaction conditions: indole (1 mmol), aldehyde (2 mmol), peroxide (6 mmol for ^tBuOOH and 4 mmol for the others), PTSA (0.1 mmol, 10 mol %) in CH₂Cl₂, at rt, air. Isolated yield. ^bThe reaction was carried out for 2 h.

corresponding *N*-(α -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*-(α -peroxy)indole under the standard conditions (see details in Supporting Information). Similar results were observed in the α -azide peroxide construction reaction,⁹ 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.⁹

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^{a,b}

^aReaction performed in air. ^bYields based on ¹H 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*-(α -peroxy)indole. On the other hand, although nucleophilic addition of indole to aldehyde has been reported,¹⁷ no reaction was observed in the above-mentioned 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 α -azide peroxide (Scheme 3).⁹ Nucleophilic addition of indole to the peroxycarbenium ion then produces the *N*-(α -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.¹⁸ Although a naturally occurring carbazole peroxide compound has not been discov-

Scheme 3. Proposed Mechanism

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*-(α -peroxy)carbazole molecule. On the other hand, while the *N*-(α -alkoxyalkyl)amines, including *N*-(α -alkoxyalkyl)carbazoles, have been synthesized and found to have good bactericidal and fungicidal activity,¹⁹ to our best knowledge, the *N*-(α -peroxy)carbazole has not been mentioned yet. As shown in Scheme 4, the condensation processed smoothly under

Scheme 4. Synthesis of *N*-(α -Peroxycarbazole from the Three-Component Condensation Reaction^a

^aReaction conditions: carbazole (1 equiv), aldehyde (2 equiv), peroxide (5.5 M in decane, 6 equiv), PTSA (0.1 mmol, 10 mol %) in CH₂Cl₂, at rt, air. Isolated yield.

standard conditions, and the desired *N*-(α -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 *t*-BuOOH was replaceable with safer *t*-BuOOH solution in decane, favorable for future scale-up of the synthetic process. The *N*-(α -*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-5*H*-dibenzo[*b,f*]azepine, 1*H*-benzo[*d*]imidazole, and 1*H*-benzo[*d*]imidazole, were found to be unreactive under the standard conditions.

In conclusion, a facile chemoselective methodology for the synthesis of *N*-(α -peroxy)indole and *N*-(α -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 α -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

182 references such as “Prudent Practices in the Laboratory” (The
183 National Academies Press, Washington, DC. 2011; the full text
184 can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654).

186 ■ ASSOCIATED CONTENT

187 ■ Supporting Information

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

190 Experimental procedures, characterization data, and NMR
191 spectra (PDF)

192 X-ray crystallographic data for **4c** (CIF)

193 ■ AUTHOR INFORMATION

194 Corresponding Authors

195 *E-mail: xinbo.wang@kaust.edu.sa.

196 *E-mail: zhiping.lai@kaust.edu.sa.

197 Notes

198 The authors declare no competing financial interest.

199 ■ ACKNOWLEDGMENTS

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

203 ■ REFERENCES

- 204 (1) (a) Maneerat, W.; Ritthiwigrom, T.; Cheenpracha, S.; Promgool,
205 T.; Yossathera, K.; Deachathai, S.; Phakhodee, W.; Laphookhieo, S. J.
206 *Nat. Prod.* **2012**, 75, 741–746. (b) Kaushik, N. K.; Kaushik, N.; Attri, P.;
207 Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, 18,
208 6620–6662. (c) Casteel, D. A. *Nat. Prod. Rep.* **1999**, 16, 55–73.
209 (d) Žmitek, K.; Zupan, M.; Iskra, J. *Org. Biomol. Chem.* **2007**, 5, 3895–
210 3908.
211 (2) (a) Wright, C. W.; Addae-Kyereme, J.; Breen, A. G.; Brown, J. E.;
212 Cox, M. F.; Croft, S. L.; Gökçek, Y.; Kendrick, H.; Phillips, R. M.; Pollet,
213 P. L. *J. Med. Chem.* **2001**, 44, 3187–3194. (b) Lisgarten, J. N.; Coll, M.;
214 Portugal, J.; Wright, C. W.; Aymami, J. *Nat. Struct. Biol.* **2002**, 9, 57–60.
215 (3) (a) Posner, G. H.; O'Neill, P. M. *Acc. Chem. Res.* **2004**, 37, 397–
216 404. (b) Wu, Y. *Acc. Chem. Res.* **2002**, 35, 255–259.
217 (4) (a) Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. *Angew.*
218 *Chem., Int. Ed.* **2003**, 42, 5274–5293. (b) Weisman, J. L.; Liou, A. P.;
219 Shelat, A. A.; Cohen, F. E.; Kiplin Guy, R.; DeRisi, J. L. *Chem. Biol. Drug*
220 *Des.* **2006**, 67, 409–416. (c) Ginsburg, H.; Deharo, E. *Malar. J.* **2011**, 10,
221 S1. (d) Ridley, R. G. *Nature* **2002**, 415, 686–693. (e) Fidock, D. A.;
222 Rosenthal, P. J.; Croft, S. L.; Brun, R.; Nwaka, S. *Nat. Rev. Drug Discovery*
223 **2004**, 3, 509–520.
224 (5) Sundar, N.; Jacob, V.; Bhat, S. V.; Valecha, N.; Biswas, S. *Bioorg.*
225 *Med. Chem. Lett.* **2001**, 11, 2269–2272.
226 (6) (a) Hsu, S. F.; Plietker, B. *ChemCatChem* **2013**, 5, 126–129.
227 (b) Schweitzer-Chaput, B.; Klusmann, M. *Eur. J. Org. Chem.* **2013**,
228 2013, 666–671. (c) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu,
229 K. R. *Org. Lett.* **2013**, 15, 1092–1095. (d) Yu, H.; Shen, J. *Org. Lett.*
230 **2014**, 16, 3204–3207.
231 (7) Schmidt, U.; Häusler, J. *Angew. Chem., Int. Ed. Engl.* **1976**, 15, 497–
232 498.
233 (8) Zheng, W.; Wojtas, L.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2010**, 49,
234 6589–6591.
235 (9) Pramanik, S.; Ghorai, P. *Org. Lett.* **2013**, 15, 3832–3835.
236 (10) (a) Yamazaki, M.; Fujimoto, H.; Kawasaki, T. *Chem. Pharm. Bull.*
237 **1980**, 28, 245–254. (b) Yamazaki, M.; SUZUKI, S.; MIYAKI, K. *Chem.*
238 *Pharm. Bull.* **1971**, 19, 1739–1740.
239 (11) (a) Cole, R.; Kirksey, J.; Moore, J.; Blankenship, B.; Diener, U.;
240 Davis, N. *Applied microbiology* **1972**, 24, 248–250. (b) Cole, R. J.;
241 Kirksey, J. W. *J. Agric. Food Chem.* **1973**, 21, 927–929. (c) Fayos, J.;

- Lokensgard, D.; Clardy, J.; Cole, R. J.; Kirksey, J. W. *J. Am. Chem. Soc.* **1974**, 96, 6785–6787. (d) Cole, R. J.; Kirksey, J. W.; Cox, R. H.; Clardy, 243
J. *J. Agric. Food Chem.* **1975**, 23, 1015–1018. (e) Yoshizawa, T.; 244
Morooka, N.; Sawada, Y.; Udagawa, S.-I. *Appl. Environ. Microbiol.* **1976**, 245
32, 441–442. 246
(12) Uramoto, M.; Tanabe, M.; Hirotsu, K.; Clardy, J. *Heterocycles* 247
1982, 17, 349–354. 248
(13) NISHIYAMA, M.; KUGA, T. *Jpn. J. Pharmacol.* **1986**, 40, 481– 249
489. 250
(14) Steffan, N.; Grundmann, A.; Afiyatullo, S.; Ruan, H.; Li, S.-M. 251
Org. Biomol. Chem. **2009**, 7, 4082–4087. 252
(15) (a) Wang, X. Process for the preparation of α -indoleamino peroxy 253
acetal compounds. Patent Appl. CN104610125A, 2015. (b) Wang, X. 254
Part III: Synthetic Studies towards Fumitremorgin A. Ph.D Thesis, 255
Peking University, 2012. 256
(16) Feng, Y.; Holte, D.; Zoller, J.; Umemiya, S.; Simke, L. R.; Baran, P. 257
S. J. Am. Chem. Soc. **2015**, 137, 10160–10163. 258
(17) (a) Scott, M. S.; Lucas, A. C.; Luckhurst, C. A.; Prodger, J. C.; 259
Dixon, D. J. *Org. Biomol. Chem.* **2006**, 4, 1313–1327. (b) Anfinogenov, 260
V.; Filimonov, V.; Sirotkina, E. *Zh. Org. Khim.* **1978**, 14, 1723–1729. 261
(18) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, 102, 4303–4428. 262
(19) (a) Anfinogenov, V. A.; Filimonov, V. D.; Sirotkina, E. E. *Zh. Org.* 263
Khim. **1978**, 14, 1687–1693. (b) Lopatinskii, V. P.; Shekhirev, Y. P. *Izv.* 264
Tomsk. Politekh. Inst. **1965**, 136, 162–165. 265