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Oxidation of 1-benzyldihydroisoquinolines or 1-benzyltetrahydroisoquinolines with dioxygen to 1-benzoylisoquinolines

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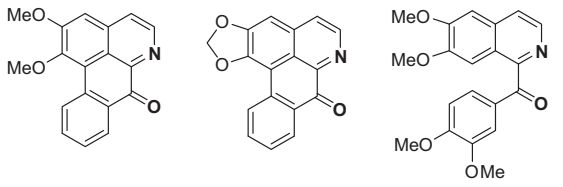
ABSTRACT

An environmental-benign methodology to synthesize 1-benzoylisoquinolines from 1-benzyl-3, 4-dihydroisoquinolines or 1-benzyl-1,2,3,4-tetrahydroisoquinolines using dioxygen as an oxidant was developed. This methodology in combination with Bischler-Napieralski reaction leads to a facile synthesis of 1-benzoylisoquinolines from phenylacetic acids and phenylethanamines.

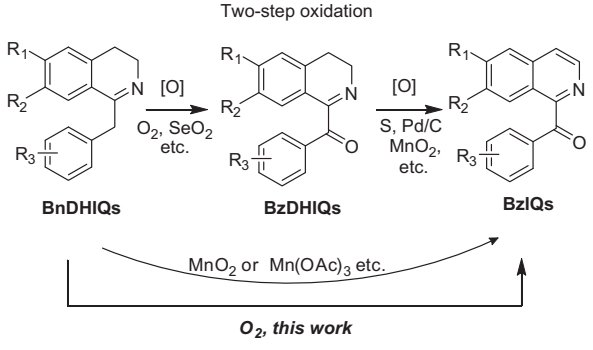
The 1-benzoylisoquinoline (BzIQ) is a common structural motif found in a variety of naturally occurring products and pharmaceuticals (Fig. 1). Some of the compounds bearing this motif display a diverse range of biological properties including antimicrobial, antimalarial, antitumor, anti-HIV activities, and antioxidant capacity.[1] For example, isoquinoline alkaloids lysicamine (**1**) and liriodenine (**2**), isolated from the bark of *Guatteria hispida*, exhibit moderate antimicrobial activity against *S. epidermidis* strain.[1j] Recently, liriodenine (**2**) was reported to possess anticancer activity as a potent CDC25 inhibitor[2a] as well as anti-arrhythmic activity by influencing the production of nitric oxide in the cell.[2b,c] Up to date, various procedures have been developed for the synthesis of this motif.[3] Among them, the most general synthetic strategy includes the following procedures: (1) condensation between phenylacetic acids and phenylethanamines via Bischler-Napieralski reaction to form 1-benzyl-3,4-dihydroisoquinolines (BnDHIQs).[4] (2) oxidation of BnDHIQs to 1-benzoyl-3, 4-dihydroisoquinolines (BzDHIQs) by several oxidizing agents, such as dioxygen,[5] selenium dioxide (SeO_2),[1a] etc. (3) Oxidation of BzDHIQs to BzIQs by sulfur,[6] IBX,[7] Pd/C[8] or activated manganese dioxide (MnO_2)[9] et al. (Scheme 1). Although such oxidations could be realized in one step by various oxidants, such as chromium trioxide (CrO_3) in pyridine,[10] MnO_2,[11] lead (IV) acetate (LTA),[12] ceric ammonium nitrate (CAN),[13] periodic acid (HIO_4),[14] iodine (I_2),[15] iodobenzene diacetate (IBD),[16] and manganese (III) acetate (MTA),[17] most of the above oxidants are toxic or hazardous metal materials, which result in waste disposal problems (Scheme 1). Therefore, developing a novel one-step oxidation using green reagent is still desirable.

We recently reported an efficient environmental-benign method for the oxidation of 2-thiazolines and 2-oxazolines to thiazoles and oxazoles,[18] in which dioxygen was used as the sole oxidant. In continuing our research on the environmental-benign oxidation of heterocycles, we herein describe a one-step oxidation of BnDHIQs and 1-benzyl-1,2,3,4-tetrahydroisoquinolines (BnTHIQs) to BzIQs using dioxygen (Scheme 1).



1 Lysicamine **2** Liriodenine **3** Papaveradine

Figure 1. Examples of 1-arylcarbonylisoquinolines.



Scheme 1. Synthesis of BzIQs via a one-step oxidation of BnDHIQs using dioxygen.

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Table 1
The screening of the reaction conditions as the sole oxidant[a]

4a **5a**

Entry	Conditions	*T* (°C)	Time (h)	Yield[b] (%)
1	DMF, K_2CO_3,O_2	80	22	55 (32[c])
2	DMF, K_2CO_3,O_2	100	22	69 (19[c])
3	DMF, K_2CO_3,O_2	120	6	85 (0[c])
4	DMF, $NaHCO_3$,O_2	80	23	88 (0[c])
5	DMF, $NaHCO_3$,O_2	100	5	87 (0[c])
6	**DMF, $NaHCO_3$, O_2**	**120**	**3**	**88 (0[c])**
7	DMF, $NaHCO_3$, air	120	6	78 (0[c])
8	EtOH, $NaHCO_3$, O_2	Reflux	22	6 (29[c], 51[d])
9	CH_3CN, $NaHCO_3$, O_2	Reflux	22	7 (86[d])
10	Pyridine, O_2	Reflux	27	26 (41[d])

[a] All reactions were performed on a 0.5 mmol scale with inorganic or organic bases (3 equiv).
[b] Isolated yields after flash chromatography.
[c] The recovery of the starting material.
[d] Isolated yields of the mono-oxidation of benzylic carbon.

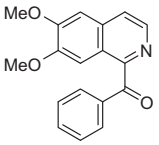
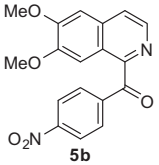
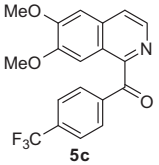
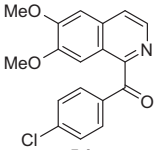
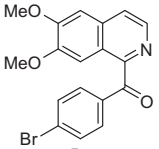
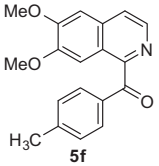
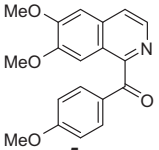
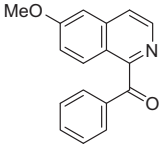
We initiated our investigation using BnDHIQ **4a** as the model substrate to establish a general procedure. **4a** was synthesized through Bischler–Napieralski reaction from 3,4-dimethoxylphenylethanamine and phenylacetic acid. A series of reaction conditions were then screened and the results were summarized in Table 1. When the reaction was conducted in DMF at 80 °C and 100 °C for 22 h, the desired product BzIQ **5a** was obtained in 55% and 69% yields, respectively, and most of the unreacted **4a** could be recovered (entries 1 and 2). Higher temperature remarkably shortened the reaction time to 6 h and the yield of **5a** was increased to 85% (entry 3). Interestingly, the yields of **5a** were even better when K_2CO_3 was replaced by $NaHCO_3$ (entries 4–6). Compound **4a** could be fully consumed in 3 h at 120 °C and **5a** was acquired in 88% yields (entry 6). It is worth noting that the reaction also proceeded smoothly in air under the same condition, although prolongated reaction time was needed (entry 7). Using EtOH, CH_3CN or pyridine as solvent generated the desired product **5a** in low yield, together with the corresponding mono-oxidative product as a major product (entries 8–10).

With the optimized condition in hand, the substrate scope of BnDHIQs with various substituents was explored (Table 2). As can be seen, a series of substrates (**4a**–**4n**) could be converted into the corresponding products (**5a**–**5n**) under the optimized condition in less than 8 h (entries 1–12). Moderate to good yields of the corresponding products could be obtained for the substrates bearing various benzyl groups (entries 1, 3–8, 10–14). However, relatively low yields of the corresponding products were obtained for the substrates with 4-nitrobenzyl group at 1-postion (entries 2 and 9).

Having demonstrated that BnDHIQs could be oxidized to BzIQs, we continued to exploit the one-step oxidation of BnTHIQs to BzIQs with dioxygen. First, we synthesized twelve BnTHIQs (**6a**–**6n**) from BnDHIQs (**5a**–**5n**) through a reduction using $NaBH_4$.[20] We then tested the oxidation of BnTHIQs. To our delight, all substrates could be oxidized to the corresponding products under the same condition in moderate yields. The results in Table 3 indicate a similar pattern about the influence of substitutions on the 1-benzyl group.[21]

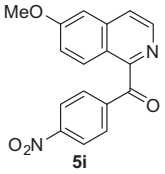
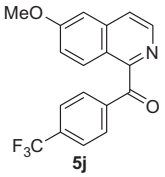
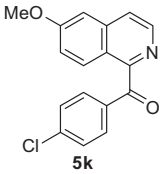
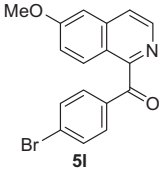
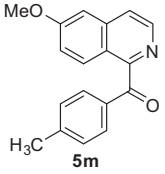
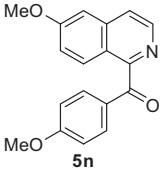
Table 2
One-step oxidation of BnDHIQs using dioxygen[a,19]

4a-n **5a-n**

Entry	Product	Yield[b] (%)
1	 **5a**	88 (3 h)
2	 **5b**	52 (7 h)
3	 **5c**	59 (3 h)
4	 **5d**	67 (3 h)
5	 **5e**	68 (3 h)
6	 **5f**	76 (4 h)
7	 **5g**	70 (3 h)
8	 **5h**	77 (7 h)

(*continued on next page*)

Table 2 (*continued*)

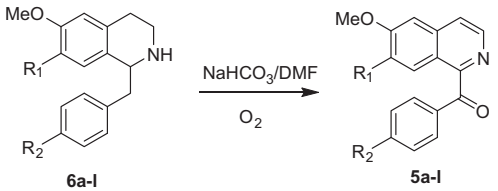
Entry	Product	Yield[b] (%)
9	 **5i**	64 (6 h)
10	 **5j**	69 (3 h)
11	 **5k**	72 (5 h)
12	 **5l**	65 (5 h)
13	 **5m**	65 (6 h)
14	 **5n**	60 (7 h)

[a] All reactions were performed in DMF on a 0.5 mmol scale with $NaHCO_3$ (3 equiv) at 120 °C.
[b] Isolated yields after flash chromatography.

Finally, we combined this methodology with Bischler–Napieralski reaction to lead to a facile synthesis of BzIQs (Scheme 2). Condensation between phenylacetic acid and phenylethanamines to form BnDHIQs (without purification), subsequent oxidation using dioxygen smoothly afforded **5a**, **5h**, and papaveradine (**3**)[23] in acceptable total yields. Thus, this procedure offers a simple route in the synthesis of BzIQs from phenylacetic acids and phenylethanamines.

In summary, we have developed the one-step oxidation of BnDHIQs and BnTHIQs to BzIQs with dioxygen as a sole oxidant in moderate to good yields. This process is milder, safer, and more environmental-benign than the established ones. This methodology combined with Bischler–Napieralski reaction could lead to a facile method for the synthesis of BzIQs from phenylacetic acids and phenylethanamines. Further investigation and synthetic application of this protocol is now underway and will be reported in due course.

Table 3
One-step oxidation of BnTHIQs using dioxygen[a,22]



6a-l **5a-l**

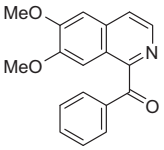
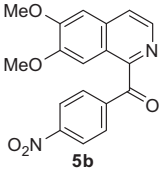
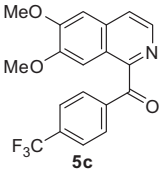
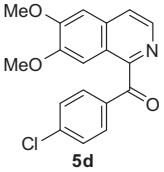
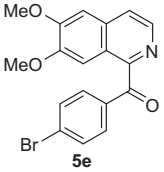
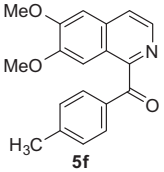
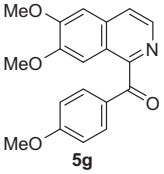
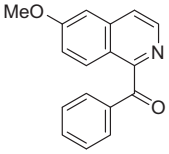
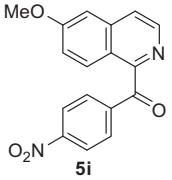
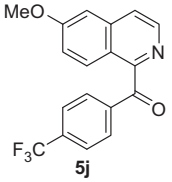
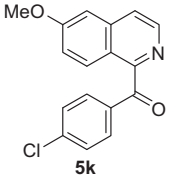
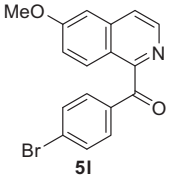
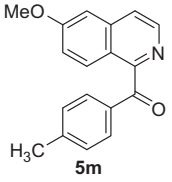
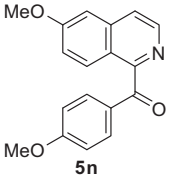
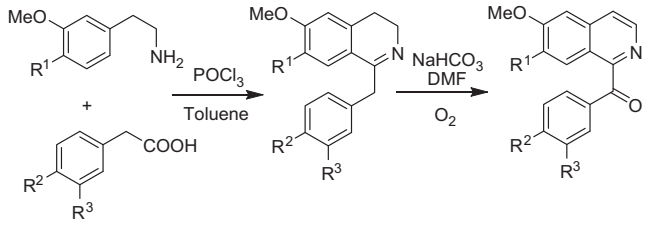
Entry	Product	Yield[b] (%)
1	 **5a**	53 (9 h)
2	 **5b**	23 (23 h)
3	 **5c**	29 (6 h)
4	 **5d**	54 (10 h)
5	 **5e**	45 (7 h)
6	 **5f**	47 (10 h)
7	 **5g**	49 (11 h)
8	 **5h**	58 (8 h)

Table 3 (*continued*)

Entry	Product	Yield[b] (%)
9	 **5i**	24 (7 h)
10	 **5j**	49 (4 h)
11	 **5k**	60 (11 h)
12	 **5l**	59 (11 h)
13	 **5m**	42 (11 h)
14	 **5n**	41 (11 h)

[a] All reactions were performed in DMF on a 0.5 mmol scale with $NaHCO_3$ (3 equiv) at 120 °C.

[b] Isolated yields after flash chromatography.



5a R^1=OMe, R^2=R^3=H (65%)
5h R^1=R^2=R^3=H (54%)
3 R^1=R^2=R^3=OMe (57%)

Scheme 2. Facile synthesis of BzIQs from phenylacetic acids and arylethanamines.

Acknowledgments

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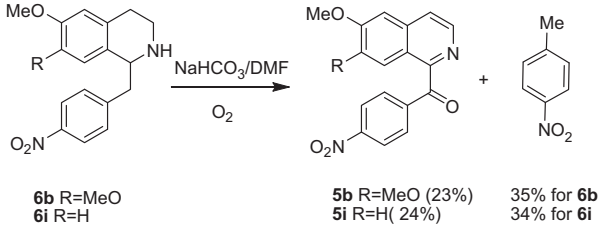
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.058.

References and notes

1. (a) Chen, C.; Zhu, Y. F.; Liu, X. J.; Lu, Z. X.; Xie, Q.; Ling, N. *J. Med. Chem.* **2001**, *44*, 4001; (b) Bermejo, A.; Andreu, I.; Suvire, F.; Leonce, S.; Caignard, D. H.; Renard, P.; Pierre, A.; Enriz, R. D.; Cortes, D.; Cabedo, N. *J. Med. Chem.* **2002**, *45*, 5058; (c) Boustie, J.; Stigliani, J. L.; Montanha, J.; Amoros, M.; Payard, M.; Girre, L. *J. Nat. Prod.* **1998**, *61*, 480; (d) Warthen, D.; Gooden, E. L.; Jacobson, M. *J. Pharm. Soc.* **1969**, *58*, 6378; (e) Stevigny, C.; Bailly, C.; Quetin-Leclercq, J. *Curr. Med. Chem.* **2005**, *5*, 173; (f) Chen, K. S.; Wu, Y. C.; Teng, C. M.; Ko, F. N.; Wu, T. S. *J. Nat. Prod.* **1997**, *60*, 645; (g) Tang, H.; Wei, Y. B.; Zhang, C.; Ning, F. X.; Qiao, W.; Huang, S. L.; Ma, L.; Huang, Z. S.; Gu, L. Q. *Eur. J. Med. Chem.* **2009**, *44*, 2523; (h) Hsieh, T. J.; Chang, F. R.; Chia, Y. C.; Chen, C. Y.; Chiu, H. F.; Wu, Y. C. *J. Nat. Prod.* **2001**, *64*, 616; (i) Costa, E. V.; Marques, F. A.; Pinheiro, M. L. B.; Vaz, N. P.; Duarte, M. C. T.; Delarmelina, C.; Braga, R. M.; Maia, B. H. L. N. S. *J. Nat. Prod.* **2009**, *72*, 1516; (j) Costa, E. V.; Pinheiro, M. L.; Barison, A.; Campos, F. R.; Salvador, M. J.; Maia, B. H. L. N. S.; Cabral, E. C.; Eberlin, M. N. *J. Nat. Prod.* **2010**, *73*, 1180.
2. (a) Woo, S. H.; Reynolds, M. C.; Sun, N. J.; Cassady, J. M.; Snapka, R. M. *Biochem. Pharmacol.* **1997**, *54*, 467; (b) Hsieh, T. J.; Liu, T. Z.; Chen, C. L.; Tsao, D. A.; Lu, F. J.; Syu, Y. H.; Hsieh, P. Y.; Hu, H. S.; Chang, T. T.; Chen, C. H. *Food Chem. Toxicol.* **2005**, *43*, 1117; (c) Chang, W. L.; Chung, C. H.; Wu, Y. C.; Su, M. J. *Nitric Oxide* **2004**, *11*, 307.
3. (a) Yen, Y. H.; Chu, Y. H. *Tetrahedron Lett.* **2004**, *45*, 8137; (b) Pal, B.; Jaisankar, P.; Giri, V. S. *Synth. Commun.* **2003**, *33*, 2339; (c) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *68*, 980; (d) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306; (e) Yu, X.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 895.
4. (a) Bischler, A.; Napieralski, B. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903; (b) Bergstrom, F. W. *Chem. Rev.* **1944**, *35*, 77.
5. Awuah, E.; Capretta, A. *J. Org. Chem.* **2010**, *75*, 5627.
6. Still, W. J.; McNulty, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1329.
7. Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4077.
8. (a) Buchs, P.; Brossi, A. *Helv. Chim. Acta* **1981**, *64*, 681; (b) Bembenek, M. E.; Abell, C. W.; Chrisey, L. A.; Rozwadowska, M. D.; Gessner, W.; Brossi, A. *J. Med. Chem.* **1990**, *33*, 147; (c) Batra, S.; Sabnis, Y. A.; Rosenthal, P. J.; Avery, M. A. *Bioorg. Med. Chem.* **2003**, *11*, 2293.
9. Janin, Y. L.; Roulland, E.; Beurdeley-Thomas, A.; Decaudin, D.; Monneret, C.; Poupon, M. F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 529.
10. (a) Granchelli, F. E.; Neumeyer, J. L. *Tetrahedron* **1974**, *30*, 3701; (b) Pai, B. R.; Shanmugasundaram, G. *Tetrahedron* **1965**, *21*, 2579.
11. Yang, S. S.; Huang, W. Y.; Lin, L. C.; Yeh, P. Y. *Chemistry (Taipei)* **1961**, 144.
12. LTA Lenz, G. R.; Costanza, C. *J Org. Chem.* **1988**, *53*, 1176.
13. Kuo, R. Y.; Chang, F. R.; Wu, C. C.; Patnam, R.; Wang, W. Y.; Du, Y. C.; Wu, Y. C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2789.
14. Philipov, S.; Ivanovska, N.; Nikolova, P. *Pharmazie* **1998**, *53*, 694.
15. Zhang, Y.; Zhong, X.; Zheng, A.; Hu, X.; Zuo, J.; Hu, L. *Bioorg. Med. Chem.* **2007**, *15*, 988.
16. Reddy, G. C. *Tetrahedron Lett.* **1995**, *36*, 1001.
17. Singh, O. V.; Huang, W.; Chen, C.; Lee, S. S. *Tetrahedron Lett.* **2007**, *48*, 8166.
18. Oxidation of 2-thiazolines, see: (a) Huang, Y.; Gan, H.; Li, S.; Xu, J.; Wu, X.; Yao, H. *Tetrahedron Lett.* **2010**, *51*, 1751; (b) Oxidation of 2-oxazolines, 2010, submitted.
19. *Typical experimental procedure for oxidation of BnDHIQs by dioxygen*. To a solution of BnDHIQ **4a** (141 mg, 0.5 mmol) in anhydrous DMF (2 mL) was added $NaHCO_3$ (126 mg, 1.5 mmol). The reaction mixture was heated to 120 °C with an O_2 balloon and stirred for 3 h. The resulting solution was diluted with ethyl acetate and the solution was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford 128 mg (88%) of BzIQ **5a** as a white solid. Mp: 131–132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47 (d, J = 5.5 Hz, 1H), 7.96 (d, J = 7.6 Hz, 2H), 7.67 (d, J = 5.5 Hz, 1H), 7.64–7.58 (m, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.15 (s, 1H), 4.06 (s, 3H), 3.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.4, 153.2, 153.0, 151.2, 140.1, 137.1, 134.1, 133.4, 130.9, 128.4, 123.0, 121.6, 104.9, 104.0, 56.1; MS(ESI) m/z 294.1 $[M+H]^+$.
20. Huang, W. J.; Singh, O. V.; Chen, C. H.; Lee, S. S. *Helv. Chim. Acta* **2004**, *87*, 167.

21. The relatively low yields of the corresponding products were due to the decomposition of the BnTHIQs. For example,



6b R=MeO
6i R=H

5b R=MeO (23%) 35% for **6b**
5i R=H(24%) 34% for **6i**

22. *Typical experimental procedure for oxidation of BnTHIQs by dioxygen*. To a solution of BnTHIQ **6a** (142 mg, 0.5 mmol) in anhydrous DMF (2 mL) was added $NaHCO_3$ (126 mg, 1.5 mmol). The reaction mixture was heated to 120 °C with an O_2 balloon and stirred for 9 h. The resulting solution was diluted with ethyl acetate and the solution was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to provide 78 mg (53%) of BzIQ **5a** as a white solid.
23. Wu, W. N.; Huang, C. H. *Chin. Pharm. J.* **2006**, *58*, 41.