ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: L. Wu, Y. Hao, Y. Liu and Q. Wang, *Chem. Commun.*, 2019, DOI: 10.1039/C9CC07791J.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C9CC07791J

COMMUNICATION

Visible-Light-Induced Intramolecular sp³ C–H Oxidation of 2-Alkyl-Substituted Benzamides for Synthesis of Functionalized Iminoisobenzofurans

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Lingang Wu [a], Yanan Hao [a], Yuxiu Liu [a] and Qingmin Wang *[a,b]

We have developed a protocol for the synthesis of functionalized iminoisobenzofurans by means of visible-light-induced intramolecular cyclization reactions of 2-alkyl-substituted benzamides. This step-economical protocol, which involves intramolecular sp³ C-O bond formation, features mild reaction conditions, exclusive chemoselectivity, and high yields.

Isobenzofurans are prevalent in biologically active compounds and natural products.[1] In addition, these heterocycles can serve as multipurpose synthetic building blocks and as precursors of reactive intermediates. Iminoisobenzofurans are particularly important members of this class of compounds, and the development of methods for their synthesis has attracted considerable research attention.[2] Iminoisobenzofurans are generally synthesized by Pd-catalyzed coupling of 2-alkylbenzamides[3] or arynes formed *in situ*,[4] by Ag- and Au-catalyzed cycloisomerization of 2-alkylbenzohydroxamic acid derivatives,[5] and by cyclization of olefinic amides.[6]

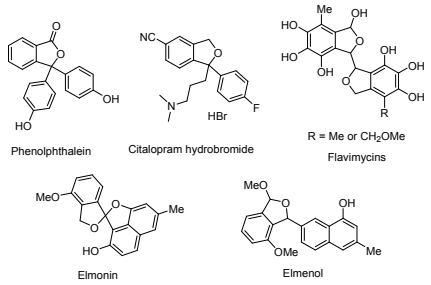
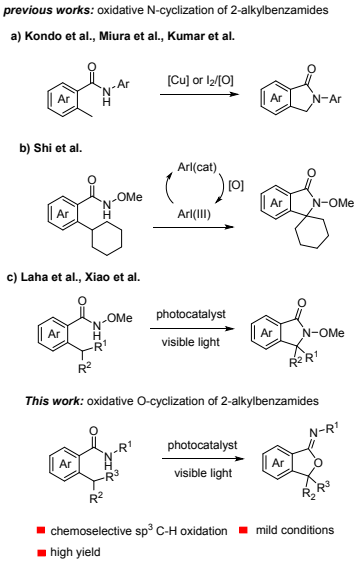


Figure 1. Examples of medicinally active compounds and natural products containing isobenzofurans.

Scheme 1. Syntheses of isoindolinones and iminoisobenzofurans by intramolecular selective aminative or oxidative cyclization of 2-alkyl-substituted benzamides.



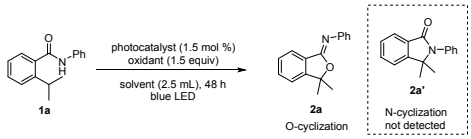
The use of selective intramolecular oxidative amination reactions of the sp³ C-H bonds of 2-alkyl-substituted benzamides for the synthesis of isoindolinones has been thoroughly studied. The research groups of Kondo and Miura separately reported the development of copper-catalyzed sp³ C-H aminative cyclization reactions of 2-alkyl-*N*-arylbenzamides for the synthesis of *N*-aryl-isoindolinones.[7] In addition, Kumar's group successfully utilized 2-alkyl-*N*-arylbenzamides in transition-metal-free selective intramolecular oxidative sp³ C-N coupling reactions to generate *N*-aryl-isoindolinones[8] (Scheme 1a). Furthermore, in an elegant study, Shi and co-workers efficiently constructed C–N bonds via iodoarene-catalyzed stereospecific intramolecular sp³ C-H amination reactions of 2-cyclohexyl-*N*-methoxybenzamides (Scheme 1b).[9] In recent years, visible light photocatalysis has emerged as powerful technique to facilitate activation of organic molecules and engineer new chemical processes since the seminal studies from the groups of MacMillan, Yoon, and Stephenson.[10] Such a catalytic strategy has also proven to be efficient accesses to N-radicals[11] and the application of visible light for photocatalytic activation of amides represents a valuable approach to facilitate the

[a] State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, People's Republic of China. E-mail: wangqm@nankai.edu.cn
[b] Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, People's Republic of China

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

formation of amidyl radicals.[12] The groups of Laha, Xiao, and Zeng reported visible-light-catalyzed or electrochemical benzylic sp^3 C-H amination reactions of 2-alkyl-*N*-methoxybenzamides (Scheme 1c).[13] The C–H amidation through an amidyl radical has been studied well, however, to our knowledge, chemoselective intramolecular sp^3 C-H O-cyclization, as opposed to N-cyclization, under mild conditions with high yields has not been reported. Herein, we disclose a protocol for visible-light-induced intramolecular sp^3 C-H oxidation of 2-alkyl-substituted benzamides.

Table 1. Optimization of reaction conditions for O-cyclization of 2-isopropyl-*N*-phenylbenzamide.[a]



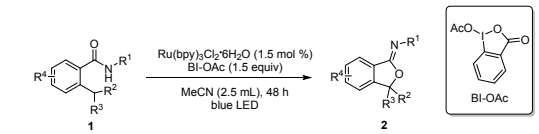
entry	photocatalyst	oxidant	solvent	yield (%)[b]
1	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	BI-OAc	DCE	51
2	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	BI-OAc	MeOH	13
3	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	BI-OAc	DMSO	24
4	**$Ru(bpy)_3Cl_2{\cdot}6H_2O$**	**BI-OAc**	**MeCN**	**81**
5	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	BI-OH	MeCN	10
6	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	BIO	MeCN	0
7	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	O_2	MeCN	0
8	$[Ir(dtbbpy)(ppy)_2][PF_6]$	BI-OAc	MeCN	47
9	Mes-Acr-$Me^+ClO_4^-$	BI-OAc	MeCN	20
10	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	BI-OAc (1.25 equiv)	MeCN	74
11	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	BI-OAc (1.75 equiv)	MeCN	80
12	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	BI-OAc	MeCN (2.0 mL)	63
13	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	BI-OAc	MeCN (3.0 mL)	78
14[c]	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	BI-OAc	MeCN	65, 81
15	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	-	MeCN	0
16	—	BI-OAc	MeCN	0
17[d]	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	BI-OAc	MeCN	0

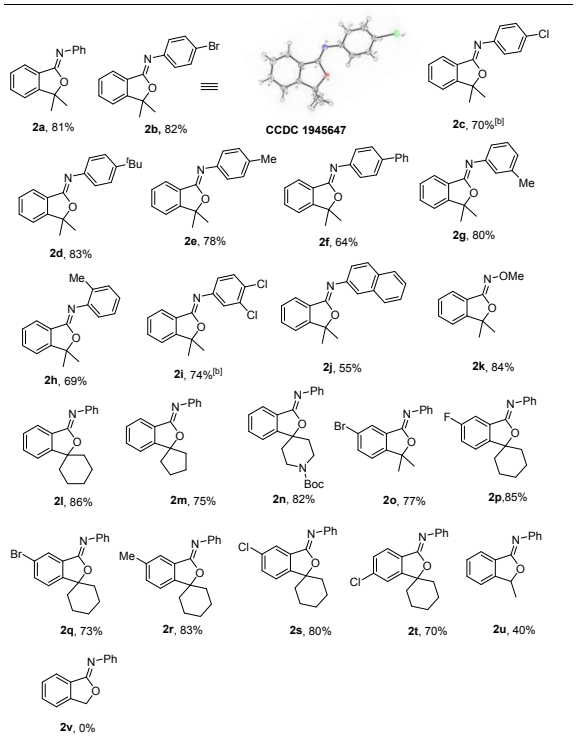
[a] General conditions, unless otherwise noted: **1a** (0.25 mmol), photocatalyst (0.00375 mmol), oxidant (0.375 mmol), and solvent (2.5 mL) at room temperature under Ar atmosphere. DCE, dichloroethane; BI-OAC, acetoxybenziodoxole. [b] Isolated yields are given. [c] Reaction time is 36 h and 60 h, respectively. [d] Reaction performed in the absence of light.

View Article Online DOI: 10.1039/C9CC07791J

We began our study by evaluating the oxidative intramolecular cyclization of 2-isopropyl-*N*-phenylbenzamide (**1a**) in several solvents with various oxidants and photocatalysts (Table 1). We were delighted to find that in the presence of 1.5 mol% of $Ru(bpy)_3Cl_2{\cdot}6H_2O$ as a photocatalyst and acetoxybenziodoxole (BI-OAc) as an oxidant, reaction of **1a** in dichloroethane under irradiation with a 5 W blue LED proceeded smoothly and chemoselectively via an O-cyclization pathway to give iminoisobenzofuran **2a** in 51% yield (entry 1). None of the N-cyclization product, 3,3-dimethyl-2-phenylisoindolin-1-one (**2a'**), was detected. Screening of various solvents (MeOH, DMSO, and MeCN) revealed that MeCN was the most effective (entries 1–4). None of the other oxidants we tested afforded the desired product in good yield (entries 5–7). Evaluation of two other photocatalysts showed that $Ru(bpy)_3Cl_2{\cdot}6H_2O$ was superior (entries 8 and 9). The changes of amount of solvent or oxidant could not give a better result (entries 10–13). Similarly, prolonging or shortening the reaction time did not lead to a better yield (entry 14). Control experiments demonstrated that the reaction failed to proceed in the absence of oxidant, photocatalyst, or light (entries 15–17).

Table 2. Substrate scope with respect to the 2-alkylbenzamide.[a]



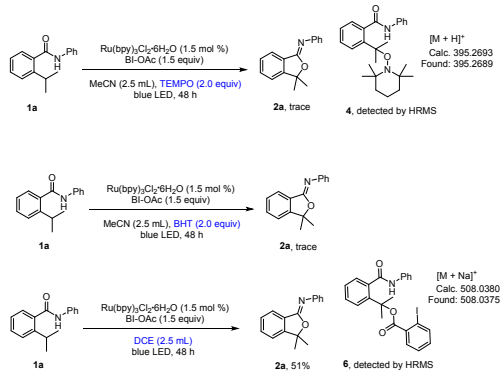


[a] Reactions were performed on a 0.25 mmol scale, and isolated yields are given. [b] Reaction time is 60 h.

View Article Online
DOI: 10.1039/C9CC07791J

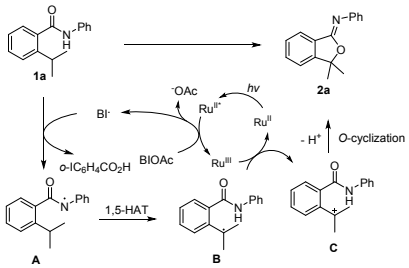
With the optimal conditions established (Table 1, entry 4), we investigated the substrate generality and the limitations of the reaction (Table 2). First, we examined the effect of substituents on the phenyl group attached to the N atom of *o*-alkylbenzamides **1**. Substrates bearing *para* substituents with various electronic properties were well tolerated, affording (*Z*)-3,3-dimethyl-*N*-phenylisobenzofuran-1(3*H*)-imines **2b**–**2f** in good to excellent yields. For **2c**, notably, a good yield could be obtained with an extended reaction time. The configuration of product **2b** was unambiguously determined by means of X-ray crystallography.[14] Substrates with *meta*- and *ortho*-substituents, afforded oxidative products **2g** and **2h**, respectively, in good yields. Benzamides with a polysubstituted phenyl group (**1i**), a naphthyl group (**1j**), and a methoxy group (**1k**) on the N atom were also compatible with this protocol. In addition, oxidation reactions of substrates with cyclic tertiary C–H bonds (**1l** and **1m**) worked well. Notably, a Boc-protected piperidyl substrate was acceptable, affording spiro product **2n** in 82% yield. We next evaluated the influence of substituents on the phenyl ring of the benzamide moiety. Substrates bearing a methyl group or a halogen atom produced iminoisobenzofurans **2o**–**2t** in good yields. A substrate with a secondary C–H bond, that is, 2-ethyl-substituted compound **1u**, underwent oxidation to afford **2u**, but the yield was relatively low (40%). However, a substrate containing a primary C–H bond (**1v**) was incompatible with this protocol; most of the starting material was recovered unchanged. To explore the synthetic utility of the protocol, we transformed imino-group-containing product **2a** to 3,3-dimethylisobenzofuran-1(3*H*)-one by means of acid hydrolysis.[6b]

Scheme 2. Mechanistic experiments.



Having explored the substrate scope, we turned our attention to the mechanism (Scheme 2). Control experiments showed that the oxidative cyclization of amide **1a** was impeded by the presence of a radical inhibitor (2,2,6,6-tetramethyl-1-piperidinyloxy [TEMPO] or butylated hydroxytoluene [BHT]); most of the starting material was recovered unchanged. Byproducts **4** and **5** were observed by mass spectrometry (see the Supporting Information for details), suggesting that an alkyl radical had been generated. In addition, when we carried out the reaction in DCE (Table 1, entry 1), intermolecular oxidation product **6** was detected by mass spectrometry, suggesting that an alkyl cation had been generated.

Scheme 3. Proposed mechanism.



On the basis of these observations and literature reports, we propose that the reaction was initiated by single-electron transfer from photoexcited $Ru(bpy)_3^{2+}$* to BI-OAc to generate $Ru(bpy)_3^{3+}$ and BI· (Scheme 3).[15] Amidyl radical **A** were generated when amide **1a** was oxidized by BI·.[12a] Subsequently, a 1,5-hydrogen atom transfer (HAT) reaction provided C-centered radical **B**.[16] Radical **B** was oxidized by $Ru(bpy)_3^{3+}$ to afford carbocation intermediate **C**, and then nucleophilic O-cyclization delivered target product **2a**.[6c],[6d] Whereas the exact mechanism of chemoselectivity O-cyclization is unclear at the moment, mild condition and longer reaction time may indicate that O-cyclization is advantageous process thermodynamically compared with N-cyclization.

In conclusion, we have developed a protocol for visible-light-induced intramolecular sp^3 C–H oxidation reactions of a variety of 2-alkyl-substituted benzamides to afford functionalized iminoisobenzofurans. This mild reaction exhibited exclusive chemoselectivity and high yields, indicating that it has great potential utility for the preparation of a wide variety of iminoisobenzofurans. Further studies aimed at evaluating the bioactivity of the products and broadening the synthetic applications are in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the National Key Research and Development Program of China (2018YFD0200100) and the National Natural Science Foundation of China (21732002, 21672117, 21772102) for generous financial support for our programs.

Notes and references

1 (a) J. K. Harper, A. M. Arif, E. J. Ford, G. A. Strobel, J. A. Porco, D. P. Tomer, K. L. Oneill, E. M. Heider and D. M. Grant, *Tetrahedron*, 2003, **59**, 2471–2476; (b) Y. J. Kwon, M. J. Sohn, C. J. Kim, H. Koshino and W. G. Kim, *J. Nat. Prod.*, 2012, **75**, 271–274; (c) M. S. Abdelfattah, M. A. Arai and M. Ishibashi, *Chem. Pharm. Bull.*, 2016, **64**, 668–675; (d) M. K. Peters and R. Herges, *Beilstein J. Org. Chem.*, 2017, **13**, 2659–2662; (e) Z. Z. Gao, C. Wang, L. G. Zhou, C. H. Yuan, Y. M. Xiao, and H. C Guo, *Org. Lett.*, 2018, **20**, 4302–4305.

2 For a review, see: F. Wang, Y.-D. Wang, L.-C. Cai, Z.-W. Miao and R.-Y. Chen, *Chin. J. Org. Chem.*, 2008, **28**, 1523–1533.

3 (a) J.-J. Wang, Z.-Y. Yan, C.-M. Tan, X. Wang, F. Li, G.- L. Gao, X.-M. Chen and W.-S. Wu, *Synlett*, 2011, 1863–1870; (b) B. Yao, C. Jaccoud, Q. Wang and J. Zhu, *Chem. - Eur. J.*, 2012, **18**, 5864–5868; (c) Y. Madich, R. Alvarez and J. M. Aurrecoechea, *Eur. J. Org. Chem.*, 2014, 6263–6271.

4 (a) H. Yoshida, H. Fukushima, J. Ohshita and A. Kunai, *Angew. Chem. Int. Ed.*, 2004, **43**, 3935–3938; (b) K. M. Allan, C. D. Gilmore and B. M. Stoltz, *Angew. Chem. Int. Ed.*, 2011, **50**, 4488–4491; (c) J. Li, S. Noyori, K. Nakajima and Y. Nishihara, *Organometallics*, 2014, **33**, 3500–3507.

5 (a) X. Bantreil, A. Bourderioux, P. Mateo, C. E. Hagerman, M. Selkti, E. Brachet and P. Belmont, *Org. Lett.*, 2016, **18**, 4814–4817; (b) D. Ding, T. Mou, J. Xue and X. Jiang, *Chem. Commun.*, 2017, **53**, 5279–5282.

6 (a) J.-F. Zhao, X.-H. Duan, H. Yang and L.-N. Guo, *J. Org. Chem.*, 2015, **80**, 11149–11155; (b) H. Yang, X.-H. Duan, J.-F. Zhao and L.-N. Guo, *Org. Lett.,* 2015, **17**, 1998–2001; (c)Z.-C. Liu, Q.-Q. Zhao, J. Chen, Q, Tang, J.-R. Chen and W.-J. Xiao, *Adv. Synth. Catal.*, 2018, **360**, 2087–2092; (d) A. Bunescu, Q. Wang and J. Zhu, *Chem. - Eur. J.*, 2014, **20**, 14633-14636.

7 (a) K. Nozawa-Kumada, J. Kadokawa, T. Kameyama and Y. Kondo, *Org. Lett.*, 2015, **17**, 4479–4481; (b) C. Yamamoto, K. Takamatsu, K. Hirano and M. Miura, *J. Org. Chem.*, 2016, **81**, 7675–7684.

8 A. Verma, S. Patel, Meenakshi, A. Kumar, A. Yadav, S. Kumar, S. Jana, S. Sharma, Ch. D. Prasad and S. Kumar, *Chem. Commun.*, 2015, **51**, 1371–1374.

9 C. Zhu, Y. Liang, X. Hong, H. Sun, W.-Y. Sun, K. N. Houk and Z. Shi, *J. Am. Chem. Soc.,* 2015, **137**, 7564-7567.

10 (a) D. A. Nicewicz and D. W. C. MacMillan, *Science*, 2008, **322**, 77–80; (b) M. A. Ischay, M. E. Anzovino, J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 2008, **130**, 12886–12887; (c) J. M. Narayanam, J. W. Tucker and C. R. Stephenson, *J. Am.Chem. Soc.*, 2009, **131**, 8756–8757.

11 For selected reviews, see: (a) J.-R. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, *Chem. Soc. Rev.*, 2016, **45**, 2044–2056; (b) M. Karkas, *ACS Catal.*, 2017, **7**, 4999–5022; (c) D. P. Hari and B. Konig, *Chem. Commun.*, 2014, **50**, 6688–6699.

12 (a) G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu and R. R. Knowles, *Nature*, 2016, **539**, 268–271; (b) J. C. Chu and T. Rovis, *Nature*, 2016, **539**, 272–275; (c) W. Yuan, Z. Zhou, L. Gong and E. Meggers, *Chem. Commun.*, 2017, **53**, 8964–8967; (c) E. M. Dauncey, S. P. Morcillo, J. J. Douglas, N. S. Sheikh and D. Leonori, *Angew. Chem. Int. Ed.*, 2018, **57**, 744–748; (d) J. Davies, T. D. Svejstrup, D. Fernandez Reina, N. S. Sheikh and D. Leonori, *J. Am. Chem. Soc.*, 2016, **138**, 8092–8095; (e) W. Yuan, Z. Zhou, L. Gong and E. Meggers, *Chem. Commun.*, 2017, **53**, 8964–8967; (f) C. Martinez and K. Muñiz, Angew. Chem., Int. Ed., 2015, 54, 8287–8291; (g) E. A. Wappes, S. C. Fosu, T. C. Chopko and D. A. Nagib, *Angew. Chem., Int. Ed.*, 2016, **55**, 9974–9978; (h) M. A. Short, J. M. Blackburn and J. L. Roizen, *Angew. Chem., Int. Ed.*, 2018, **57**, 296–299.

13 (a) G. Pandey and R. Laha, *Angew. Chem. Int. Ed.,* 2015, **54,** 14875-14879; (b) D.-M. Yan, Q.-Q. Zhao, L. Rao, J.-R. Chen and W.-J. Xiao, *Chem. - Eur. J.*, 2018, **24**, 16895–16901; (c) S. Zhang, L. J. Li, M. Y. Xue, R. K. Zhang, K. Xu and C. C. Zeng, *Org. Lett.*, 2018, **20**, 3443–3446.

14 CCDC 1945647 (**2b**) contains supplementary crystallographic data for this paper.

15 (a) N. Wang, Q. S. Gu, Z.-L. Li, Z. Li, Y.-L. Guo, Z. Guo and X.-Y. Liu, *Angew. Chem. Int. Ed.*, 2018, **57**, 14225-14229; (b) H. Huang, G. Zhang and Y. Chen, *Angew. Chem. Int. Ed.*, 2015, **54**, 7872-7876; (c) G.-X. Li, C. A. Morales-Rivera, Y. Wang, F. Gao, G. He, P. Liu and G. Chen, *Chem. Sci.*, 2016, **7**, 6407-6412.

16 (a) F. G. Bordwell and G.-Z. Ji, *J. Am. Chem. Soc.*, 1991, 113, 8398-8401; (b) J.-P. Cheng and Y. Y. Zhao, *Tetrahedron*, 1993, **49**, 5267-5276; (c) J. J. Brocks, H.-D. Beckhaus, A. L. J. Beckwith and C. Ruchardt, *J. Org. Chem.*, 1998, **63**, 1935-1943.

View Article Online
DOI: 10.1039/C9CC07791J