



Cite this: *RSC Adv.*, 2021, 11, 29372

Visible-light-driven cascade radical cyclization toward the synthesis of α -carbonyl alkyl-substituted benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives†

Jing Liu,^{‡ab} Hong-Li Huang,^{‡c} Chen Wang,^b Yinghua Li,^b Huaqiang Li,^b Honggang Hu,^b Shipeng He,^b Hua Tang^{*b} and Fei Gao^{id}^{*b}

Received 5th August 2021
Accepted 24th August 2021

DOI: 10.1039/d1ra05936j

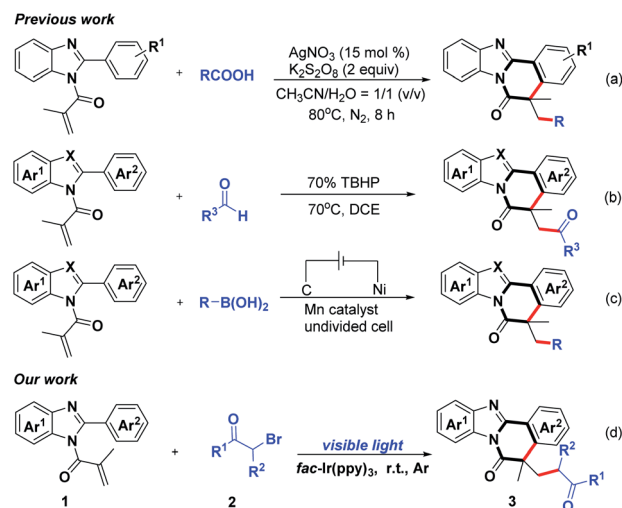
rsc.li/rsc-advances

A visible-light-driven cascade radical cyclization process of *N*-methacryloyl-2-phenylbenzimidazole has been established with α -carbonyl alkyl bromide. This protocol provides an efficient and practical method for the synthesis of various α -carbonyl alkyl-substituted benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones in outstanding yields, mild reaction conditions and excellent functional group tolerance.

Benzimidazo-fused polycyclic motifs, especially benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives, have been frequently found in numerous pharmaceutical molecules, natural products and synthetic materials.^{1–7} As a consequence, considerable efforts have been made to develop efficient methods for the preparation of benzimidazo-fused polycyclic compounds. Among them, the cascade radical cyclization strategies have attracted special attention from chemists. In 2019, Yu and co-workers realized the construction of benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones *via* silver-catalyzed decarboxylative radical cascade cyclization (Scheme 1a).⁸ A metal-free oxidative acylation/cyclization of *N*-methacryloyl-2-phenylbenzimidazole with aryl aldehydes has also been found by Reddy's group (Scheme 1b).⁹ At the same time, Aiwen Lei's laboratory has devoted effort to the development of Mn-catalyzed electrochemical radical cascade cyclization reaction toward the preparation of benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones (Scheme 1c).¹⁰ Despite important breakthroughs in the radical cascade cyclization, room still exists for developing a visible-light-driven pathway to acquire benzimidazo-fused polycyclic compounds under milder reaction conditions.

Recently, visible-light-mediated photoredox catalysis has arguably gained considerable momentum due to its inherent green, excellent functional group tolerance, safe and availability.^{11–17} α -Carbonyl alkyl bromide, which are readily available and inexpensive chemical reagents, could be successfully converted into α -carbonyl alkyl radicals for rapidly constructing

C–C bonds under the irradiation of visible light.^{18–23} During the past decades, the applications on the visible-light-promoted cascade radical cyclization process for the synthesis of complex polycyclic hydrocarbons have been reported.^{24,25} In contrast to the previous achievements in the formation of benzimidazo-fused polycyclic compounds, research on visible-light-induced α -carbonyl alkylation to construct benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones remains scarce. Inspired by these researches, we designed a novel visible-light-driven cascade radical cyclization for the synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinoline tetracyclic skeleton, in which α -carbonyl alkyl radical generated from the corresponding bromide could undergo intermolecular radical addition to the C–C double



Scheme 1 Reported synthesis of benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives and our strategy.

^aDepartment of Chemistry, College of Sciences, Shanghai University, No. 99 Shangda Road, Shanghai 200444, China

^bInstitute of Translation Medicine, Shanghai University, Shanghai, 200444, China

^cCollege of Chemistry and Chemical Engineering, Liaocheng University, Liaocheng, Shandong, 252059, China

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra05936j

‡ These authors contributed equally to this work.

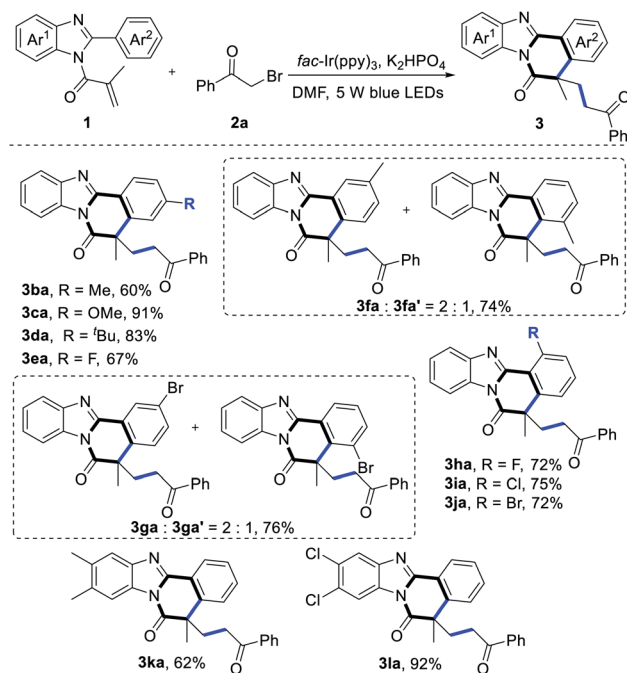


bond, followed by the formation of intramolecular C–C bond, to synthesize the corresponding cyclization compounds (Scheme 1d).

At the outset, we chose *N*-methacryloyl-2-phenylbenzimidazole (**1a**) and 2-bromoacetophenone (**2a**) as the model substrates. Optimization of the reaction conditions was explored by irradiating a mixture of model substrates, base and photocatalyst under Ar atmosphere using 5 W blue LEDs at room temperature (Table 1). In the presence of *fac*-Ir(ppy)₃ (5% mol), K₂HPO₄ (2.0 equiv.), and CH₃CN (1 mL), the target product **3aa** was afforded in 60% isolated yield (entry 1). Next, the reaction was investigated using diverse photocatalysts. Unfortunately, some common photocatalysts, such as Ir[dF(CF₃)ppy]₂(dtbpy)PF₆, Ru(ppy)₃Cl₂ and EosinY showed low catalytic activity (entries 2–4). Subsequently, further screening on the solvent revealed that DMF could provide a slightly improvement in reaction efficiency (entries 5–7). Gratifying, examination on the bases showed that 2,6-lutidine was the ideal choice and the desired product **3aa** was obtained in 88% yield (entries 8–15). In addition, control experiments confirmed that the photocatalyst and visible light were essential for this transformation (entries 16–17).

With the optimized reaction conditions in hand, we then surveyed the scope of substrate **1**. As shown in Table 2, a series of *N*-methacryloyl-2-phenylbenzimidazoles could undergo cascade radical cyclization to synthesize the desired products successfully. Different substituents, including –F, –Cl, –Br, –Me,

Table 2 Scope of *N*-methacryloyl-2-phenylbenzimidazoles **1**^a



^a Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), *fac*-Ir(ppy)₃ (0.005 mmol), K₂HPO₄ (0.2 mmol), dry DMF (1 mL), 5 W blue LEDs, r. t., Ar, 16 h. Isolated yield.

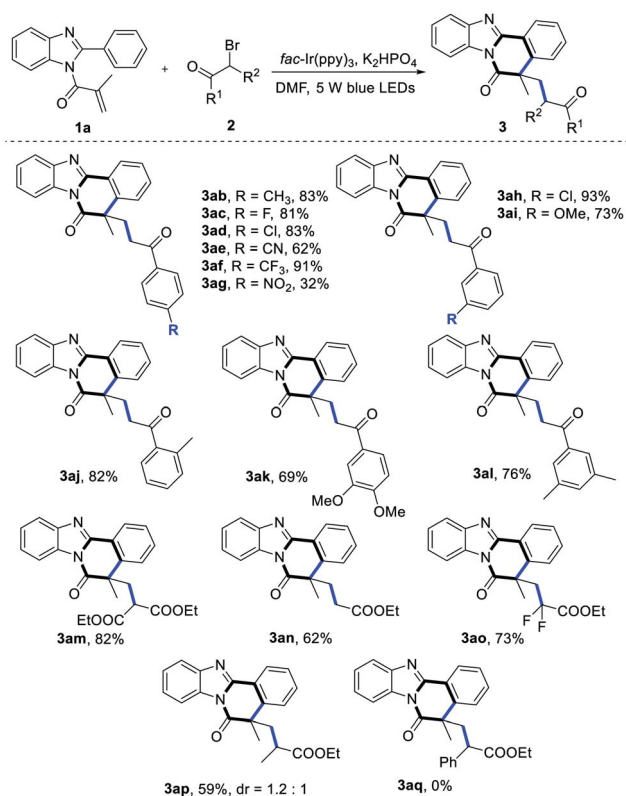
Table 1 Optimization of reaction conditions^a

Entry	Photocatalyst	Base	Solvent	Yield ^b [%]
1	<i>fac</i> -Ir(ppy) ₃	K ₂ HPO ₄	CH ₃ CN	60
2	Ir[dF(CF ₃)ppy] ₂ (dtbpy)PF ₆	K ₂ HPO ₄	CH ₃ CN	15
3	Ru(ppy) ₃ Cl ₂	K ₂ HPO ₄	CH ₃ CN	Trace
4	EosinY	K ₂ HPO ₄	CH ₃ CN	Trace
5	<i>fac</i> -Ir(ppy) ₃	K ₂ HPO ₄	DMF	70
6	<i>fac</i> -Ir(ppy) ₃	K ₂ HPO ₄	DMSO	59
7	<i>fac</i> -Ir(ppy) ₃	K ₂ HPO ₄	DCM	67
8	<i>fac</i> -Ir(ppy) ₃	NaHCO ₃	DMF	65
9	<i>fac</i> -Ir(ppy) ₃	Na ₂ CO ₃	DMF	<10
10	<i>fac</i> -Ir(ppy) ₃	Cs ₂ CO ₃	DMF	Trace
11	<i>fac</i> -Ir(ppy) ₃	KH ₂ PO ₄	DMF	50
12	<i>fac</i> -Ir(ppy) ₃	2,6-Lutidine	DMF	88
13	<i>fac</i> -Ir(ppy) ₃	Pyridine	DMF	11
14	<i>fac</i> -Ir(ppy) ₃	DBU	DMF	13
15	<i>fac</i> -Ir(ppy) ₃	DABCO	DMF	41
16 ^c	<i>fac</i> -Ir(ppy) ₃	K ₂ HPO ₄	DMF	0
17 ^d	—	K ₂ HPO ₄	DMF	0

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), *fac*-Ir(ppy)₃ (0.005 mmol), base (0.2 mmol), solvent (anhydrous, 1 mL), Ar, 5 W blue LEDs, room temperature (r.t.), 16 h. ^b Isolated yield. ^c In the dark. ^d No photocatalyst.

–OMe, and –^tBu at the 2-benzene ring of benzimidazole were well tolerated (**3ba–3ja**), especially substrate **1c** with strong electron-donating –OMe group transformed to the product **3ca** in 91% yield. Notably, steric hindrance didn't affect the reaction efficiency, employing *ortho*-, *meta*- and *para*-substituted 2-arylbenzimidazoles as the starting materials, the cyclization products were obtained in good yields. When the *meta*-position of the 2-benzene ring of benzimidazole was substituted by a –Me or –Br group (**1f** and **1g**), the regioisomers were afforded in a ratio of 2 : 1. As expected, in the case of substrates **1k** and **1l**, good yields of the desired products were formed (**3ka** and **3la**, 62% and 92%, respectively).

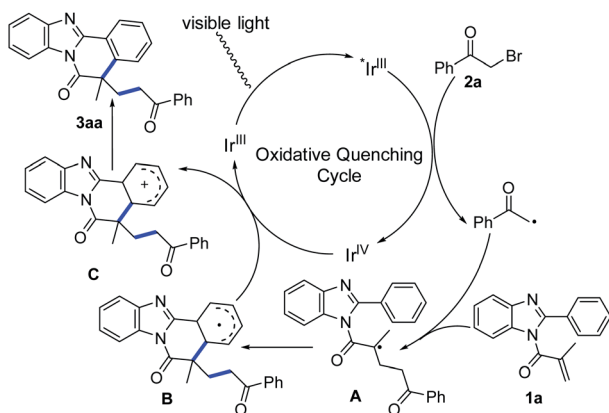
To further gain more information about this protocol, using **1a** as the model substrate, we turned our attention to explore the scope of α -carbonyl alkyl bromide derivatives **2** (Table 3). First, a wide range of 2-bromoacetophenones were examined (**2b–2l**). To our delight, 2-bromoacetophenones with electron-donating substituents (–Me, –OMe) or electron-withdrawing groups (–F, –Cl, –CF₃, –CN) at the *ortho*-position/*meta*-position/*para*-position of the benzene ring were all competent partners in this transformation (**3ab–3aj**), especially compound **2f** and **2h** successfully led to the desired products **3af** and **3ah** in 91% and 93% yields, respectively. By contrast, 2-bromoacetophenone bearing strong electron-drawing NO₂ group at the *para*-position of the benzene ring afforded the expected product **3ag** in 32% yield. Next, when 2-bromoacetophenones **2k** or **2l** was applied as the oxidant, this reaction proceeded smoothly

Table 3 Substrate scope of compound 2^a

^a Reaction conditions: 1a (0.1 mmol), 2 (0.2 mmol), fac-Ir(ppy)_3 (0.005 mmol), K_2HPO_4 (0.2 mmol), dry DMF (1 mL), 5 W blue LEDs, r. t., Ar, 16 h. Isolated yield.

and the corresponding cyclization products (3ak–3al) were obtained in good yields. In addition, α -bromoalkyl esters 2m–2p were also suitable reaction partners, delivering the corresponding products 3am–3ap in moderate to good yields. Finally, it seemed that this reaction conditions were not ideal for α -bromoalkyl esters 2q.

Based on the above experimental results and literature reports,^{26–28} a plausible reaction mechanism for this visible-light-induced cascade cyclization was described in Scheme 2.



Scheme 2 Possible mechanism.

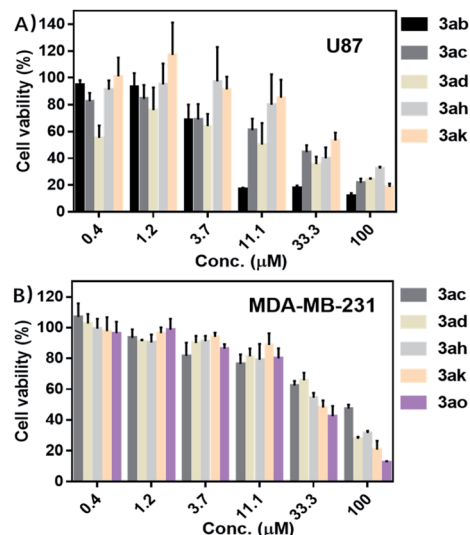


Fig. 1 (A) Cytotoxicity of 3ab, 3ac, 3ad, 3ah and 3ak against U87 cells for 72 h. (B) Cytotoxicity of 3ac, 3ad, 3ah, 3ak and 3ao against MDA-MB-231 cells for 72 h.

Upon irradiation with visible light, the ground-state $[\text{fac-}^{\text{III}}\text{Ir(ppy)}_3]$ was excited to the excited-state $[\text{fac-}^{\text{III}}\text{Ir(ppy)}_3]^*$, which was readily reduced by 2-bromoacetophenone (2a) to produce the corresponding α -carbonyl alkyl radical specie. Following intermolecular addition with the C–C double bond of the substrate 1a, the resulting radical intermediate A underwent radical addition cyclization to form the intermediate B. Subsequently, the intermediate B was oxidized by $[\text{fac-}^{\text{IV}}\text{Ir(ppy)}_3]^*$ to produce the carbocation C, which finally transformed to the eventual product 3aa after rapid deprotonation.

Benzimidazo[2,1- α]isoquinolin-6(5H)-one derivatives have been reported as potential pharmaceutical molecules with antitumor activity.^{29,30} Then, we explored the cell cytotoxicity of several representative cyclization products against MDA-MB-231 cells (human breast cancer cells) and U87 cells (human glioblastoma cells). As shown in Fig. 1, these products almost showed definite antitumor activities, especially the IC₅₀ of compound 3ab was 4.228 μM against U87 cells. It is very hopeful that these α -carbonyl alkyl-substituted benzimidazo[2,1- α]isoquinolin-6(5H)-ones show outstanding antitumor activity after further structural optimization.

In conclusion, we have developed a simple and efficient photoredox-assisted cascade radical cyclization method to synthesize a series of α -carbonyl alkyl-containing benzimidazo[2,1- α]isoquinolin-6(5H)-ones, some of which exhibited definite anticancer ability against U87 cells and MDA-MB-231 cells. Additional research on the improvement of biological activity is currently underway in our group. Moreover, this transformation shows the advantages of mild reaction conditions, good functional group compatibility and acceptable to excellent yields. We believe that this method will be widely used in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of Shanghai (No. 1ZR1422600), the Science and Technology Project of Nantong, China (No. MS22019026), and Shanghai Sailing Program (No. 20YF1414100).

References

- 1 C. Pan, C. Yuan and J.-T. Yu, *Org. Biomol. Chem.*, 2021, **19**, 619–626.
- 2 X.-X. Guo, D.-W. Gu, Z. Wu and W. Zhang, *Chem. Rev.*, 2015, **115**, 1622–1651.
- 3 G. Yadav and S. Ganguly, *Eur. J. Med. Chem.*, 2015, **97**, 419–443.
- 4 L.-Y. Xie, J. Qu, S. Peng, K.-J. Liu, Z. Wang, M.-H. Ding, Y. Wang, Z. Cao and W.-M. He, *Green Chem.*, 2018, **20**, 760–764.
- 5 Y. Li, J. Zhu, H. Xie, S. Li, D. Peng, Z. Li, Y. Wu and Y. Gong, *Chem. Commun.*, 2012, **48**, 3136–3138.
- 6 G. Meng, H.-Y. Niu, G.-R. Qu, J. S. Fossey, J.-P. Li and H.-M. Guo, *Chem. Commun.*, 2012, **48**, 9601–9603.
- 7 E. Moriarty, M. Carr, S. Bonham, M. P. Carty and F. Aldabbagh, *Eur. J. Med. Chem.*, 2010, **45**, 3762–3769.
- 8 K. Sun, S.-J. Li, X.-L. Chen and Y. Liu, *Chem. Commun.*, 2019, **55**, 2861–2864.
- 9 R. Boora, G. Ravi kumar and B. V. Subba Reddy, *Org. Biomol. Chem.*, 2019, **17**, 9627–9630.
- 10 Y. Yuan, Y. Zheng, B. Xu, J. Liao, F. Bu, S. Wang, J. Hu and A. Lei, *ACS Catal.*, 2020, **10**, 6676–6681.
- 11 J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102–113.
- 12 C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363.
- 13 C. Wang, P. H. Dixneuf and J. F. Soulé, *Chem. Rev.*, 2018, **118**, 7532–7585.
- 14 L. Zou, P. Li, B. Wang and L. Wang, *Chem. Commun.*, 2019, **55**, 3737–3740.
- 15 Y.-P. Wu, M. Yan, Z.-Z. Gao, J.-L. Hou, H. Wang, D.-W. Zhang, J. Zhang and Z.-T. Zhang, *Chin. Chem. Lett.*, 2019, **30**, 1383–1386.
- 16 Y. Kong, W. Xu, X. Liu and J. Weng, *Chin. Chem. Lett.*, 2020, **31**, 3245–3249.
- 17 W. Ou, R. Zou, M. Han, L. Yu and C. Su, *Chin. Chem. Lett.*, 2020, **31**, 1899–1902.
- 18 X. Yong, Y.-F. Han, Y. Li, R.-J. Song and J.-H. Li, *Chem. Commun.*, 2018, **54**, 12816–12819.
- 19 W. Dong, Y. Yuan, X. Gao, M. Keranmu and W. Li, *J. Org. Chem.*, 2019, **84**, 1461–1467.
- 20 Q. Li, Y. Yin, Y. Li, J. Zhang, M. Huang, J. K. Kim and Y. Wu, *Org. Chem. Front.*, 2019, **6**, 3238–3243.
- 21 P. Gandeepan, J. Koeller, K. Korvorapun, J. Mohr and L. Ackermann, *Angew. Chem., Int. Ed.*, 2019, **58**, 9820–9825.
- 22 B. Zhao, Z. Li, Y. Wu, Y. Wang, J. Qian, Y. Yuan and Z. Shi, *Angew. Chem., Int. Ed.*, 2019, **131**, 9548–9552.
- 23 H.-L. Huang, J.-Y. Du, Q.-L. Li, F. Gao and C.-L. Ma, *J. Org. Chem.*, 2020, **85**, 3963–3972.
- 24 F.-L. Zeng, K. Sun, X.-L. Chen, X.-Y. Yuan, S.-Q. He, Y. Liu, Y.-Y. Peng, L.-B. Qu, Q.-Y. Lv and B. Yu, *Adv. Synth. Catal.*, 2019, **361**, 5176–5181.
- 25 B. Wang, L. Zou, L. Wang, M. Sun and P. Li, *Chin. Chem. Lett.*, 2021, **32**, 1229–1232.
- 26 D. Lu, Y. Wan, L. Kong and G. Zhu, *Org. Lett.*, 2017, **19**, 2929–2932.
- 27 L.-L. Mao, D.-G. Zheng, X.-H. Zhu, A.-X. Zhou and S.-D. Yang, *Org. Chem. Front.*, 2018, **5**, 232–236.
- 28 Y. Yuan, W. Dong, X. Gao, X. Xie and Z. Zhang, *Org. Lett.*, 2019, **21**, 469–472.
- 29 L. W. Deady and T. Rodemann, *Aust. J. Chem.*, 2001, **54**, 529–534.
- 30 X. Wang and A. B. Fulp, WO2005002503A2, 2005.

