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Redox-neutral decarboxylative photocyclization of anthranilic acids

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A mild metal-, catalyst-, and oxidant-free photoredox neutral system has been found to efficiently enable intramolecular decarboxylative cyclization of anthranilic acids. This facile protocol provides an alternative method for the synthesis of carbazoles. Mechanistic studies reveal a key photoinduced 6π -electrocyclization process and formic acid was released as the sole byproduct.

Carboxylic acids are cheap, stable, and versatile raw materials that have been widely employed in organic synthesis and related studies. Decarboxylative couplings of carboxylic acids have proved to be a viable strategy for diverse alkylations and arylations.¹ To improve the reactivity of carboxylic acids, prefunctionalizations are frequently performed to transform them into ester, thioester, or amide derivatives, which allow a smooth oxidative addition of a catalytically active low-valent metal species into the C-X bonds (X = O, S, N). Recently, alkyl carboxylic N-hydroxyphthalimide esters have been used in the decarboxylative functionalization under mild metal or photocatalysis.² Direct decarboxylative couplings of carboxylic acids represent a straightforward route in molecular synthesis. To this end, transition metal catalysis has been intensively explored to find diverse efficient catalytic systems on the basis of Pd, Cu, Ag, Rh, and Ru, etc (Fig. 1a).³ Alternatively, the in situ generation of carboxylate salts was exchanged with elemental halogen to form benzoyl hypohalites which could efficiently decompose into aryl halides (Fig. 1b).⁴

Photoredox catalysis has emerged to be a powerful tool for organic synthesis.⁵ Specifically, photoinduced decarboxylation via aroyloxy radicals provides a promising platform for couplings,⁶ which, however, is known to be challenging ($k = 1.4 \times 10^6 \text{ s}^{-1}$)⁷ because of the rapid H-atom abstraction (k = 1.2

(a) transition metal catalysis



[M]: Pd, Cu, Ag, Rh, Ru, etc.

(b) benzoyl hypohalites



M: Ag, K, etc; X = Br or I

(c) photoredox catalysis



(d) decarboxylation of anthranilic acids



 $\times 10^7$ s⁻¹) or addition to arenes ($k = 2.2 \times 10^8$ s⁻¹) (Fig. 1c).⁸ In 2017, Glorius group disclosed a visible light-mediated decarboxylation of aryl carboxylic acids via a key benzoyl hypobromite intermediate that afforded a mild access to biarenes.⁹ Recently, Yoshimi and co-workers reported visibleand UV-light-induced decarboxylative radical reactions of benzoic acids using organic photoredox catalysts.¹⁰ Based on this concept, divergent arene products by addition, borylation, and reduction were generated under mild heating conditions. Given these intermolecular findings by photoinduced

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decarboxylation of benzoic acids, speculate the we intramolecular variant would proceed with much higher reactivities. Hence, we designed N-arylanthranilic acids as the model substrate to explore the ability of decarboxylative cyclization under photocatalysis. Notably, this reaction has been previously realized by a palladium-based catalytic system involving stoichiometric copper(II) salt as the oxidant.¹¹ Herein, within our continuous program on sustainable photochemical synthesis,12 we report the metal-, oxidant- and catalyst-free photocyclization of N-arylanthranilic acids, which led to facile formation of structurally useful carbazoles¹³ (Fig. 1d).

To commence our studies, the DMSO solution of N-methyl-N-arylanthranilic acid (1a) was treated with Ir(dF- $CF_3ppy)_2(dtbbpy)PF_6$ ([Ir]PF_6) as the photocatalyst (PC) and pyridine as base under blue light irradiation and air atmosphere. This reaction afforded N-methylcarbazole (2a) in 46% yield (Table 1, entry 1). This result encouraged us to screen different photocatalysts. Unfortunately, among others both 4CzIPN and Rose Bengal did not enable the decarboxylative annulations (entries 2 and 3). Unexpectedly, the reaction performed under an oxygen atmosphere completely prohibited the desired transformation (entry 4), suggesting a non-oxidative

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decarboxylation in the present carbazole formation. The result from inert atmosphere further confirmed Phis181939880 (Entry89). The use of 1.5 equiv of pyridine slightly enhanced the intramolecular decarboxylative coupling that afforded 1a in moderate yield (50% yield, entry 6). Inorganic bases such as KHCO₃ and NaHCO₃ were inferior to pyridine (entries 7 and 8). These results above indicated that the present photoinduced decarboxylative coupling of anthranilic acid probably proceeded through 6n-electrocyclization. Hence, the UV light (365 nm) was used in the absence of photocatalyst. To our delight, this catalyst-free treatment led to a good reactivity of carbazole formation (68% yield, entry 9). Then, the test of reaction media (entries 10-15) revealed that while protic solvents such as water and methanol quenched the desired transformation, others including actone, acetonitrile (MeCN), 1,4-dioxane, and ethyl acetate all enabled this reaction. We then screened a series of bases which were all found inferior to pyridine (entries 16-21). Control experiments (entries 22-25) suggested, again, that oxygen was not necessary in the UV light system. And light irradiation found to be indispensable. Finally, the yield of 2a was dramatically decreased when using 0.5 equiv. of pyridine (entry 26).

Table 1 Optimization of reaction conditions.^a

| | \sim | N N | conditions | | |
|------------------------|---------------------|---------------------------------------|--------------------|-------------|----------------|
| | Ļ | – – – – – – – – – – – – – – – – – – – | > | N | |
| | | 1a | | 2a | |
| Entry | РС | Light source | Base | Solvent | Yield $(\%)^b$ |
| 1 | [Ir]PF ₆ | Blue LEDs | pyridine | DMSO | 46 |
| 2 | 4CzIPN | Blue LEDs | pyridine | DMSO | trace |
| 3 | Rose Bengal | Blue LEDs | pyridine | DMSO | ND |
| 4^c | [Ir]PF ₆ | Blue LEDs | pyridine | DMSO | trace |
| 5^d | [Ir]PF ₆ | Blue LEDs | pyridine | DMSO | 40 |
| 6 ^e | [Ir]PF ₆ | Blue LEDs | pyridine | DMSO | 50 (46) |
| 7 | [Ir]PF ₆ | Blue LEDs | KHCO ₃ | DMSO | 46 |
| 8 | [Ir]PF ₆ | Blue LEDs | NaHCO ₃ | DMSO | 28 |
| 9 | - | UV light | pyridine | DMSO | 68 (65) |
| 10 | - | UV light | pyridine | acetone | 45 |
| 11 | - | UV light | pyridine | H_2O | ND |
| 12 | - | UV light | pyridine | MeCN | 51 |
| 13 | - | UV light | pyridine | 1,4-dioxane | 51 |
| 14 | - | UV light | pyridine | MeOH | ND |
| 15 | - | UV light | pyridine | EtOAc | 60 (58) |
| 16 | - | UV light | DBU | DMSO | 39 |
| 17 | - | UV light | Et ₃ N | DMSO | 37 |
| 18 | - | UV light | 2,6-lutidine | DMSO | 48 |
| 19 | - | UV light | DIPEA | DMSO | 34 |
| 20 | - | UV light | NaHCO ₃ | DMSO | 37 |
| 21 | - | UV light | Cs_2CO_3 | DMSO | 45 |
| 22 | - | UV light | | DMSO | 30 |
| 23^c | - | UV light | pyridine | DMSO | 35 |
| 24^d | - | UV light | pyridine | DMSO | 65 |
| 25 ^{<i>f</i>} | - | In dark | pyridine | DMSO | ND |
| 26 ^g | - | UV light | pyridine | DMSO | 55 |

^a Reaction conditions: 1a (0.2 mmol), photocatalyst (PC, 2.0 mol%) base (1.0 equiv), DMSO (2 mL), 36 W blue LED (405 nm) or 36 W UV light (365 nm), air, 48 h. [Ir]PF₆ = Ir(dF-CF₃ppy)₂(dtbbpy)PF₆. ^b Yields were determined by GC analysis using

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dodecane as the internal standard. Isolated yields were given in parentheses. ^c Under O₂ atmosphere. ^d Under N₂ atmosphere. ^e Pyridine (1.5 equiv). ^fNo light. ^g Pyridine (0.5 equiv).

With the established UV light-induced reactivity of Nmethyl-N-arylanthranilic acid in the metal- and catalyst-free decarboxylative cyclization, we subsequently probed the generality and substrate scope of this novel photochemistry (Fig. 2).

Fig. 2 Redox-neutral decarboxylative photocyclization. ^{*a*} yield of 10.0 mmol scale reaction.

With respect to the N-aryl groups (marked by red color), parasubstituted aniline moieties bearing alkyl (2a-2e), fluoro (2h), and trifluoromethoxy (2i) functionalities were compatible with this system. The corresponding decorated carbazoles were generated in generally moderate yields. Unfortunately, metasubstituted anilines exhibited poor regioselectivities. For example, the meta-methyl substrate afforded a mixture of 4,9dimethyl-9H-carbazole and 2,9-dimethyl-9H-carbazole in a total 80% yield with a 2.3:1 ratio of regioselectivity (2f), while the meta-fluoro reactant gave a 1:1 mixture of two isomers (2g). The electron properties of the functionalities attached at this aryl ring affected dramatically on the reactivity; therein, strongly electron-donating para-methoxy group was not accommodated. Subsequently, we screened a series of substrates with substituents at the benzoyl acid moiety. Fluoro anthranilic acids afforded 2j and 2k in 22% and 41% yield, respectively. Comparably, chloro reactants enhanced the yield to 46% and 70% yield, respectively. While the anthranilic acid with methoxy group delivered 2n in 38% yield, some multifunctional carbazoles were furnished in good yields (20-2q). Regarding N-substituents, other alkyls including ethyl (2r) and butyl (2s) featured good reactivities. Allyl (2t) and benzylcarbazoles (2u) could also be produced in modest yields. Four reacting sites exist when N,N-diarylanthranilic acids were used, in which this kind of reactants exhibited good efficiency, affording N-arylcarbazoles 2v-2x in satisfactory yields, with poor selectivity in the case of unsymmetric triaryl amine (2x). Notably, the effective gram-scale reaction of 1a under redoxneutral conditions mirrored the robust nature of our photochemical decarboxylative couplings (56% yield for 10.0 mmol scale).

During our studies on the substrate scope, some unexpected results including dehalogenation and demethylation were obtained (Fig. 3). The N-methyl-N-(2-fluorophenyl)anthranilic acid afforded exclusively N-methylcarbazole 2a with the flouro group completely eliminated (Fig. 3a). Dehalogenation of the para-halogen such as chloro and bromo was also observed, leading to the formation of mixtures of halocarbazoles (2z and 2aa) and 2a (Fig. 3b,c). This result may be attributed to decomposition in C-X bond of the excited intermediate with high-energy under UV light. The anthranilic acids bearing otoluidine moiety proceeded through the decarboxylative cyclization with methyl group partially eliminated. While 2methyl and 2,4-dimethyl substrates underwent decarboxylative cyclization with minor demethylation products (6:1 and 3:1, respectively, Fig. 3d,e), the 2,3-dimethylphenyl anthranilic acid afforded carbazole product via demethylation process (1:25, Fig. 3f). Mechanistically, demethylation as well as defluorination in ortho positions may occur in the decarboxylative elimination process.

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dehalogenation:

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Fig. 3 Photoinduced decarboxylative couplings along with dehalogenation and demethylation.

Decarboxylative couplings in many cases proceed under oxidative conditions via radical pathway. The control experiments under inner atmosphere (Table 1) reveal that our UV-light-induced decarboxylative cyclization of anthranilic acids is achieved in a redox-neutral reaction system. Moreover, in our photo system, the pyridine additive and DMSO solvent were dispensable, which rules out intermolecular electron transfer and hydrogen-atom transfer. Instead, the reaction initially proceeds through direct light-irradiation of substrate followed by intramolecular cycloisomerization. The addition of a radical scavenger such as TEMPO, butylated hydroxytoluene (BHT), and 1,1-diphenylethylene (DPE) had no significant influence on the reaction efficiency (Fig. 4a), which could also probably suggest a non-radical mechanism of this reaction. On the basis of some literature, we speculate a redox-neutral 6π photocyclization mechanism¹⁴ that ultimately releases formic acid as the side product (Fig. 5). Thus, the reaction mixture after competition was guardedly added dropwise to a silver ammonia solution. To our delight, a silver mirror formed on the solution surface (Fig. 4b), which suggests that formic acid was probably generated. The intramolecular kinetic isotope effect was determined to be $k_{H/D} = 1:1$ (Fig. 4c), indicating a kinetically irrelevant C-H bond cleavage. Hence, the photocyclization is probably the rate determining step. Then,

we studied the steric hindrance effect of the cyclization process by using meta-substituted anthranilic acrds10(F139/140).COWRIE methyl substrate afforded C2-cyclized product 2f as the major product, the formation o C6-participated annulation product was enhanced when using isopropyl anthranilic acid (1ae). Furthermore, C6-annulation product was exclusively generated when tert-butyl substrate was subjected to the system (1af). These results are in line with the proposed 6π photocyclization process. To determine the role of pyridine additive, we measured UV-Vis absorption of anthranilic acid 1a and its mixture with pyridine. The results reveal that the addition of pyridine reduced the absorption density of 1a in the UV light range (Fig. 4e). Hence, the pyridine additive may only play a positive role in the process of formic acid elimination. Finally, the result of light-on/off experiments rules out a radical chain reaction pathway (Fig. 4f).

(a) radical scavenger

Fig. 4 Mechanistic studies.

Fig. 5 Possible reaction mechanism.

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Notably, N-methyldiphenylamine did not work in our redoxneutral photochemical system and majority of the starting reactant was recovered. We rationally speculate that the electron-withdrawing carboxylic acid group could probably stabilize the charge polarized intermediate (**B**) that thereby enables the electrocyclization process.

Conclusions

In summary we have developed a catalyst- and oxidant-free decarboxylative photocyclization reaction of anthranilic acids under ambient temperature and air conditions. This redoxneutral protocol provides a mild alternative approach for the construction of structurally significant carbazole compounds. Generally moderate yields were obtained with tolerance of useful functional groups. Dehalogenation and some demethylation of some special substrates were unexpectedly observed, which may inspire other designation of synthesis through inner bond cleavage. Experimental results of some mechanistic studies reveal a reaction cascade involving photomediated 6π -electrocyclization and subsequent pyridinepromoted formic acid elimination.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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Notes and references

- (a) N. Rodriguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, 40, 5030-5048; (b) J. D. Weaver, A. Recio, 3rd, A. J. Grenning and J. A. Tunge, *Chem. Rev.*, 2011, 111, 1846-1913.
- (a) R. S. J. Proctor, H. J. Davis and R. J. Phipps, *Science*, 2018, 360, 419–422; (b) M.-C. Fu, R. Shang, B. Zhao, B. Wang and Y. Fu, *Science*, 2019, 363, 1429–1434; (c) C. Wang, M. Guo, R. Qi, Q. Shang, Q. Liu, S. Wang, L. Zhao, R. Wang and Z. Xu, *Angew. Chem. Int. Ed.*, 2018, 57, 15841–15846; (d) J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D. H. Bao, F. L. Wei, T. Zhou, M. D. Eastgate and P. S. Baran, *Nature*, 2017, 545, 213-218; (e) J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C. M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.*, 2016, 138, 2174-2177; (f) A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers and V. K.

Aggarwal, Science, 2017, **357**, 283-286; (g) T. Qin J. Cornella C. Li, L. R. Malins, J. T. Edwards, S. Kawamuna B. D. Cather and P. S. Baran, Science, 2016, **352**, 801-805.

- (a) L. J. Gooßen, G. Deng and L. M. Levy, *Science*, 2006, 313, 662-664;
 (b) P. J. Moon and R. J. Lundgren, *ACS Catalysis*, 2019, 10, 1742-1753;
 (c) Y. Wei, P. Hu, M. Zhang and W. Su, *Chem. Rev.*, 2017, 117, 8864-8907.
- (a) G. J. P. Perry, J. M. Quibell, A. Panigrahi and I. Larrosa, J. Am. Chem. Soc., 2017, 139, 11527-11536; (b) J. M. Quibell, G. J. P. Perry, D. M. Cannas and I. Larrosa, Chem. Sci., 2018, 9, 3860-3865.
- (a) J. Xuan and W. J. Xiao, Angew. Chem. Int. Ed., 2012, 51, 6828-6838; (b) C. K. Prier, D. A. Rankic and D. W. MacMillan, Chem. Rev., 2013, 113, 5322-5363; (c) M. Reckenthäler and A. G. Griesbeck, Adv. Synth. Catal., 2013, 355, 2727-2744; (d) M. N. Hopkinson, B. Sahoo, J. L. Li and F. Glorius, Chem. Eur. J, 2014, 20, 3874-3886; (e) D. M. Schultz and T. P. Yoon, Science, 2014, 343, 1239176; (f) N. Corrigan, S. Shanmugam, J. Xu and C. Boyer, Chem. Soc. Rev., 2016, 45, 6165-6212; (g) K. L. Skubi, T. R. Blum and T. P. Yoon, Chem. Rev., 2016, 116, 10035-10074; (h) M. Silvi and P. Melchiorre, Nature, 2018, 554, 41-49.
- (a) S. Mukherjee, B. Maji, A. Tlahuext-Aca and F. Glorius, J. Am. Chem. Soc., 2016, 138, 16200-16203; (b) N. P. Ramirez, I. Bosque and J. C. Gonzalez-Gomez, Org. Lett., 2015, 17, 4550-4553.
- I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel and P. S. Baran, *J. Am. Chem. Soc.*, 2010, 132, 13194–13196, 132, 13194-13196.
- J. Chateauneuf, J. Lusztyk and K. U. Ingold, J. Am. Chem. Soc., 1988, 110, 2886-2893.
- L. Candish, M. Freitag, T. Gensch and F. Glorius, *Chem. Sci.*, 2017, 8, 3618-3622.
- S. Kubosaki, H. Takeuchi, Y. Iwata, Y. Tanaka, K. Osaka, M. Yamawaki, T. Morita and Y. Yoshimi, *J. Org. Chem.*, 2020, 85, 5362-5369.
- Z. Y. Hu, Y. Zhang, X. C. Li, J. Zi and X. X. Guo, Org. Lett., 2019, 21, 989-992.
- 12. For recent examples of sustainable photosynthesis, see: (a) Z. Wang, Q. Liu, X. Ji, G.-J. Deng and H. Huang, ACS Catal., 2020, 10, 154-159; (b) Z. Wang, X. Ji, T. Han, G. J. Deng and H. Huang, Adv. Synth. Catal., 2019, 361, 5643-5647; (c) Z. Wang, X. Ji, J. Zhao and H. Huang, Green Chem., 2019, 21, 5512-5516; (d) M. Fu, X. Ji, Y. Li, G.-J. Deng and H. Huang, Green Chem., 2020, 22, DOI: 10.1039/d1030gc02269a; (e) X. Ji, Q. Liu, Z. Wang, P. Wang, G.-J. Deng and H. Huang, Green Chem., 2020, 22, DOI: 10.1039/d1030gc01872d; (f) L. Lu, Y. Li and X. Jiang, Green Chem., 2020, 22, DOI: 10.1039/D0GC02091E; (g) K.-J. Liu, S. Jiang, L.-H. Lu, L.-L. Tang, S.-S. Tang, H.-S. Tang, Z. Tang, W.-M. He and X. Xu, Green Chem., 2018, 20, 3038-3043; (h) Y. Li, S. A. Rizvi, D. Hu, D. Sun, A. Gao, Y. Zhou, J. Li and X. Jiang, Angew. Chem. Int. Ed. 2019, 58, 13499-13506; (i) L.-Y. Xie, T.-G. Fang, J.-X. Tan, B. Zhang, Z. Cao, L.-H. Yang and W.-M. He, Green Chem., 2019, 21, 3858-3863; (j) Y. Lang, X. Peng, C.-J. Li and H. Zeng, Green Chem., 2020, 22, DOI: 10.1039/D0GC01649G.
- (a) H.-J. Knolker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303-4427; (b) A. W. Schmidt, K. R. Reddy and H. J. Knolker, *Chem. Rev.*, 2012, **112**, 3193-3328.
- (a) S. G. Modha, A. Pothig, A. Dreuw and T. Bach, J. Org. Chem., 2019, 84, 1139-1153; (b) S. Pusch, D. Schollmeyer and T. Opatz, Org. Lett., 2016, 18, 3043-3045; (c) M. Marin, V. Lhiaubet-Vallet and M. A. Miranda, Org. Lett., 2012, 14, 1788.

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