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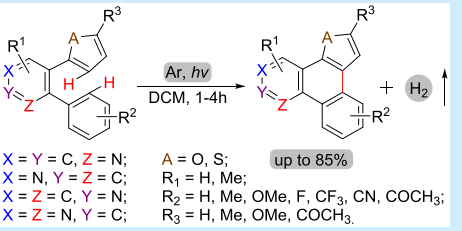
Syntheses of Benzofuranoquinolines and Analogues via Photoinduced Acceptorless Dehydrogenative Annulation of *o*-Phenylfuranylpyridines

Jinming Fan,[†] Wei Zhang,[†] Wangxi Gao, Tao Wang, Wei-Liang Duan, Yong Liang,[‡] and Zunting Zhang*

Key Laboratory of Applied Surface and Colloid Chemistry (Ministry of Education), School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710119, People's Republic of China

Supporting Information

ABSTRACT: A strategy for the syntheses of benzofuranoquinolines and its analogues via the irradiation of *o*-phenylfuranyl/thienylpyridines/pyrimidines in DCM with UV light at rt under an argon atmosphere is described. The mechanism of this reaction through the process of 6π-electrocyclization, [1,5]-hydrogen shift, and 1,3-eneamine tautomerism leading to H_2 evolution was elucidated. Notably, the syntheses of *cis*-8b-methyl-8b,13a-dihydrobenzo[*f*]-benzofuro[3,2-*h*]quinolone via the photoinduced rearrangement of 2-(3-methylbenzofuran-2-yl)-3-phenylpyridine relevant to the mechanism of this reaction highlights the importance of the developed methodology.

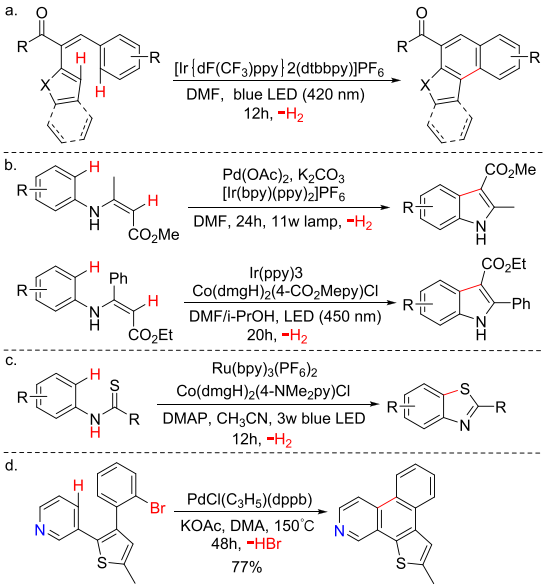


Different from all-carbon polycyclic aromatic hydrocarbons (PAHs), fused heterocyclic polycyclic aromatic hydrocarbons have a large degree of conjugation and contain heteroatoms, such as N, O, and S in the ring system, enhancing their photoluminescence properties, electron injection, and transport capabilities in organic material applications.[1] They are often used to design fluorescent chemical sensors.[2] In addition, chelation of certain fused heterocyclic aromatic hydrocarbons with metal ions by formation complexes could improve their physicochemical properties.[3] Therefore, the synthesis of fused heterocyclic aromatic compounds is of great significance.

Photoinduced organic reactions have been playing significant roles in green chemistry, especially in the construction of polycyclic aromatic compounds, which would be difficult to access with standard chemistry reactions in the ground state.[4] Furthermore, the protecting groups are not always necessary during the photochemical reactions,[5] which usually occur at rt or even below. This milder reaction condition is the advantage over thermochemical reactions. Recently, photoreactions have been used as a practical synthesis method in the fields of organic and material chemistry.[6] An intramolecular cross-coupling hydrogen evolution (CCHE) reaction is one of the good strategies to synthesize fused heterocyclic aromatic hydrocarbons, but very few examples are reported. In 2014, Reiser et al. reported an Ir-catalyzed light-induced dehydrogenative annulation of α-heteroarylchalcones for the synthesis of naphtho[2,1-*b*]furans (Scheme 1a).[7]

Also, cyclization of methyl-3-(phenylamino)but-2-enoate and ethyl-3-phenyl-3-(phenylamino)acrylate in the presence of $Pd(OAc)_2$/$[Ir(bpy)(ppy)_2]PF_6$ and $Ir(ppy)_3$/$Co(dmgH)_2$(4-CO_2Mepy)Cl gave methyl-2-methyl-1*H*-indole-3-carboxylate and ethyl-2-phenyl-1*H*-indole-3-carboxylate by the photoinduced annulation hydrogen evolution, respectively (Scheme 1b).[8,9] Moreover, irradiation of *N*-phenylbenzothioamides with blue LED in the presence of $Ru(bpy)_3(PF_6)_2$ and Co(III)-$(dmgH)_2$(4-NMe_2Py)Cl gave the dehydrocyclization product, benzothioazoles (Scheme 1c).[10] All of these transition-metal-catalyzed intramolecular CCHE reactions were carried out with

Scheme 1. Background on Photoinduced Intramolecular Cross-Coupling Hydrogen Evolution Reactions and Synthesis of Benzo[*f*]thieno[3,2-*h*]isoquinoline



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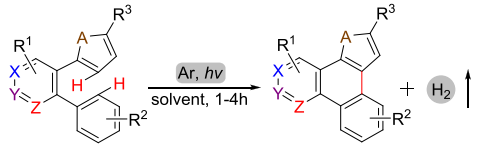
visible light irradiation at rt, and hydrogen was formed as the only byproduct.[11]

Quinoline and isoquinoline derivatives are important heterocyclic compounds and could be found in natural products and drugs.[12] Dibenzo[*f*,*h*]quinoline and its analogues, the fused polycyclic derivatives of quinoline and isoquinoline, have not been previously explored due to their limited accessibility[13] but exhibit unprecedented chemical and physical properties. For example, benzo[*f*]thieno[3,2-*h*]isoquinoline units have been used in electronic devices. The current method for the synthesis of benzo[*f*]thieno[3,2-*h*]isoquinoline requires transition metals, high temperature (150 °C), and extended reaction time (48 h), which significantly limits its application (Scheme 1d).[14]

Given our interest in photoinduced annulation[15] as well as the existence of limited literature reports on intramolecular dehydrogenative annulation, in this letter, we report a strategy for the synthesis of benzofuranoquinolines and their analogues via the photoinduced acceptorless dehydrogenative intermolecular annulation of *o*-phenylfuranylpyridine and its analogues (Scheme 2). The protocol eliminates the use of a transition

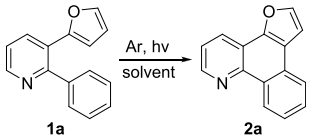
Scheme 2. Synthesis of Benzofurano/Thienoquinolines, Isoquinolines, and Quinazolines via the Photoinduced Acceptorless Dehydrogenative Intermolecular Annulation of *o*-Phenylfuranylpyridines and Analogues



metal catalyst and high temperature, proceeds smoothly without additives, and is atom-efficient. as well. In this work, based on the ^{1}H NMR monitoring and isolation of intermediates and detection of H_2, the mechanism of acceptorless dehydrogenative intermolecular annulation was disclosed for the first time. The reaction proceeded through the process of 6π-electrocyclization, [1,5]-hydrogen shift, 1,3-eneamine tautomerism, providing two inner H atoms, and H_2 evolution. Inspired by the mechanism of acceptorless dehydrogenative intermolecular annulation, *cis*-8b-methyl-8b,13a-dihydrobenzo[*f*]benzofuro[3,2-*h*]quinoline was successfully synthesized via the photorearrangement reaction of 2-(3-methylbenzofuran-2-yl)-3-phenylpyridine.

In the initial investigations, 3-(furan-2-yl)-2-phenylpyridine **1a** was chosen to screen reaction conditions, and the selected optimization results are summarized in Table 1. Irradiation of **1a** in EtOH with a high-pressure mercury lamp (500 W) under an Ar atmosphere at rt for 8 h gave benzo[*h*]furo[2,3-*f*]quinoline **2a** in 26% (Table 1, entry 1). The yields of **2a** were not significantly improved in MeOH and 95% EtOH (28% and 30%) (entries 2 and 3). Similar or even worse results were obtained in aprotic solvents, such as 1,2-dichloroethane (DCE), acetone (ACE), acetonitrile (ACN), benzene, diethyl ether (DEE), *N*,*N*-dimethylformamide (DMF), hexane, and toluene (entries 4−6 and 9−13). To our delight, the yields of **2a** were boosted to 63 and 60% in dichloromethane (DCM) and chloroform (TCM), and the reaction time was significantly shortened to 2 and 3.5 h (entries 7 and 8). It is noteworthy that irradiation of **1a** in DCM with open air led to a completely

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	time (h)[b]	yield (%)[c]
1	EtOH	8	26
2	MeOH	10	28
3	95% EtOH	8	30
4	DCE	5	33
5	ACE	12	35
6	ACN	12	40
7	DCM	2	63
8	TCM	3.5	60
9	benzene	8	19
10	DEE	10	NR
11	DMF	10	NR
12	hexane	10	trace
13	toluene	10	trace
14[d]	DCM	2	NR

[a]Irradiation of **1a** (0.25 mmol) in various solvents (50 mL, 5 mM) with a high-pressure mercury lamp (500 W) at rt. [b]Reaction time was determined by the complete consumption of **1a** as indicated by thin-layer chromatography (TLC). [c]Isolated yields. [d]In the open air.

decomposed substrate, and no **2a** was obtained (entry 14). Thus, irradiation of **1a** (5 mM) in DCM at ambient temperature under an Ar atmosphere was determined to be the optimal condition.

With the optimized condition in hand, the scope of 3-furanyl/thienyl-2-phenylpyridines **1** was examined and is shown in Scheme 3. Irradiation of 3-furanyl-2-phenylpyridines **1a**, **1d**−**1i**, **1k**, **1m**−**1p**, **1r**, and 2-phenyl-3-thienylpyridines **1b**−**1c**, **1j**, **1l**, and **1q** with a 500 W high-pressure mercury lamp gave benzofurano/thienoquinolines **2a**−**2r** in 52−82% yields. The dehydrogenative intermolecular annulation of **1** tolerated Me, OMe, COMe, F, CN, and CF_3 groups. In general, substrates with electron-withdrawing groups (COMe, F, CN, CF_3) at the R^2 position gave products in better yields than the substrates bearing an electron-donating group (Me, OMe). It is noteworthy that substrate **1m** gave the regioselective intramolecular annulation product **2m** in 82% yield. Similar regioselectivity for 3-furanyl-2-naphthalenylpyridine **1o** was observed, whereas intramolecular annulation of **2n** gave the product with less steric hindrance. Moreover, various substrates bearing an electron-donating group (methyl) at the pyridine moiety (**1p**−**1r**) also gave products in good yields.

Various pyridine and pyrimidine substrates, such as 3-(furan-2-yl)-4-phenylpyridines **3a**−**3c**, 3-phenyl-4-(thien-2-yl) pyridines **3d**, 4-(furan-2-yl)-3-phenylpyridines **4a**−**4e**,**h**, 3-phenyl-4-(thien-2-)ylpyridines **4f**,**g**, 5-(furan-2-yl)-4-phenylpyrimidines **7a**,**c**, and 4-phenyl-5-(thien-2-yl)pyrimidines **7b**,**d** were screened, and the results are summarized in Scheme 4. As the yields of **5a**−**5d** (43−66%) are almost the same as those for **2a**, **2b**, and **2d**, the position of nitrogen in the pyrimidine ring does not really affect the annulation efficiency. However, the presence of an acetyl group at the 4′-position of the phenyl ring (**3c**) decreased the yield of **5c** to 43%. Substrates **4a**−**4h** with an electron-donating group (Me, OMe) at the R^2 position gave annulation products in better yields than the substrates bearing an electron-withdrawing group (COMe, CF_3). Analogous

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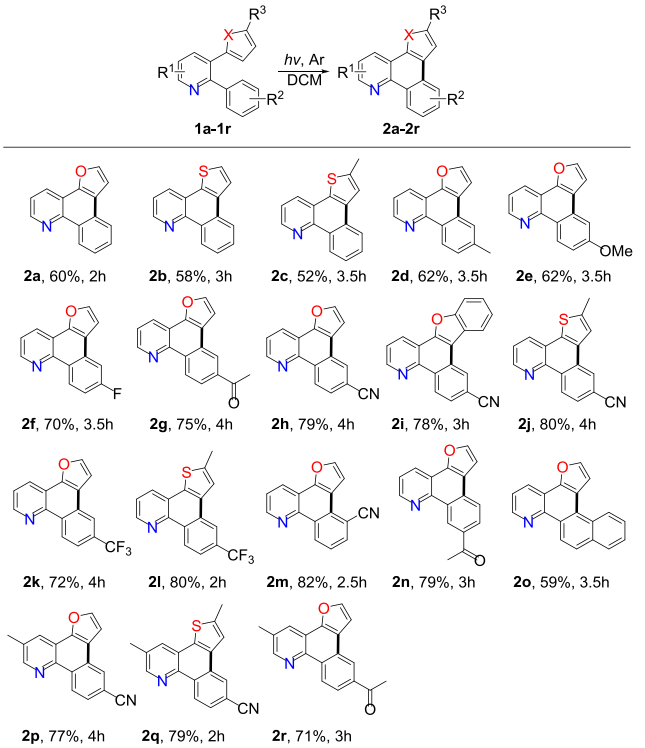
Scheme 3. Scope of Benzofurano/Thienoquinolines[a]



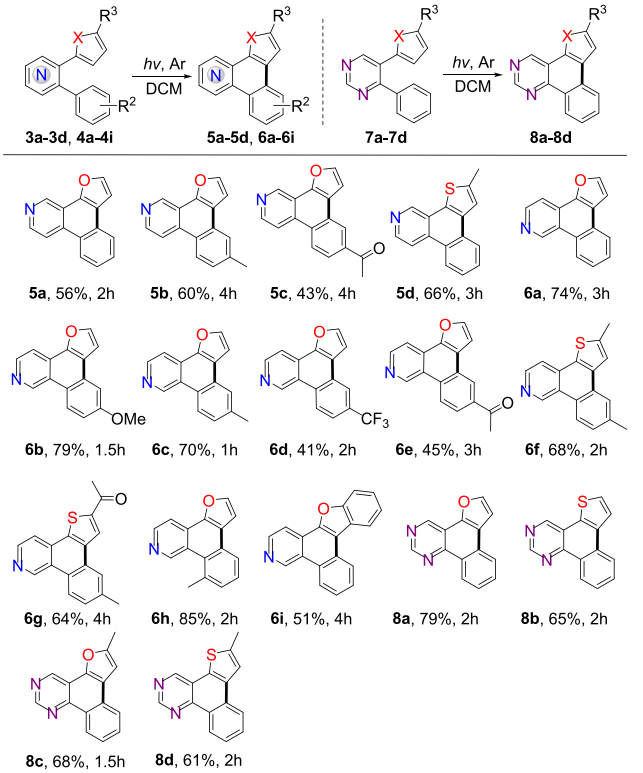
[a]Irradiation of **1** (5 mM) in DCM (50 mL) with a high-pressure mercury lamp (500 W) at rt under Ar atmosphere. Isolated yield. Reaction time was determined by the complete consumption of **1** as indicated by TLC.

treatment of 4-phenyl-5-furano/thienopyrimidines **7a−7d** under the optimal condition also yielded **8a−8d** in 61−79%.

To gain insight into the reaction mechanism, a series of experiments were designed and performed (Scheme 5). To our surprise, irradiation of 4-(benzofuran-2-yl)-3-phenylpyridine **4i** in DCM at rt under an Ar atmosphere with a high-pressure mercury lamp (500 W) for 2 h gave dehydrogenative annulation product benzo[*h*]benzofuro[2,3-*f*]isoquinoline **6i** (36%) along with the intermediate *cis*-8*b*,13*a*-dihydrobenzo[*h*]benzofuro-[2,3-*f*]isoquinoline(*cis*-8*b*,13*a*-DHBBI) **6j** (20%) (Scheme 5, eq 1). Both **6i** and **6j** were successfully isolated and characterized by NMR, HRMS, and IR. Moreover, irradiation of intermediate **6j** under the same condition for 1 h led to the formation of **6i** in an 87% yield, which resulted from elimination of a H_2 molecule from **6j**. To further monitor the formation and disappearance of intermediate **6j** in detail, the kinetic study was performed. The nuclear magnetic tube containing 10 mg of **4i** and 0.4 mL of $CDCl_3$ was irradiated with a high-pressure mercury lamp at rt under an Ar atmosphere for 0, 15, 90, and 180 min, and the ^1H NMR data were collected. As it is shown in the stacked ^1H NMR spectrum, **4i** was initially converted into intermediate **6j**, which was consumed to give dehydrogenation product **6i** (results are displayed in Supporting Information Figure S3).

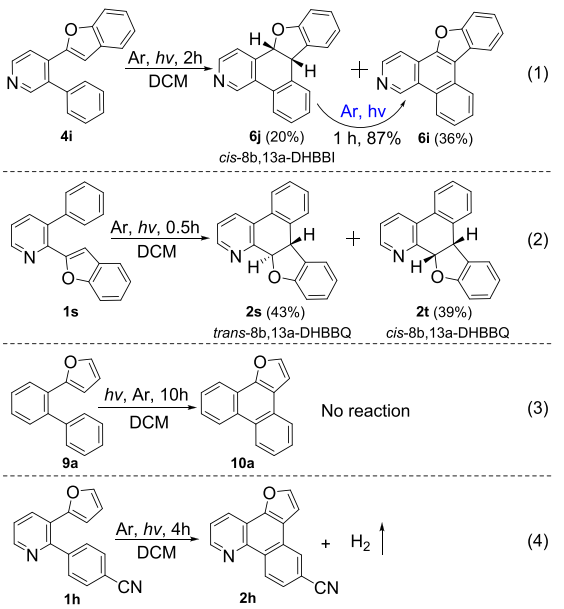
Furthermore, analogous treatment of 2-(benzofuran-2-yl)-3-phenylpyridine **1s** with a high-pressure mercury lamp for 30 min gave a separable mixture of *trans*-8*b*,13*a*-dihydrobenzo[*f*]-benzofuro[3,2-*h*]quinoline (*trans*-8*b*,13*a*-DHBBQ) **2s** and *cis*-8*b*,13*a*-dihydrobenzo[*f*]benzofuro[3,2-*h*]quinoline (*cis*-8*b*,13*a*-DHBBQ) **2t** in an 82% yield (Scheme 5, eq 2). Luckily, the structure of both **2s** and **2t** were identified by single-crystal X-ray diffraction. However, treatment of 2-([1,1′-biphenyl]-2-yl)furan

Scheme 4. Scope of Benzofurano/Thienoisoquinolines and Quinazolines[a]



[a]Irradiation of **3**, **4**, or **7** (5 mM) in DCM (50 mL) with a high-pressure mercury lamp (500 W) at rt under an Ar atmosphere. Isolated yield. Reaction time was determined by the complete consumption of **3**, **4**, or **7** as indicated by TLC.

Scheme 5. Mechanism Investigations



9a under the same conditions (500 W high-pressure mercury lamp) failed to provide dehydrogenative annulation to **10a** (Scheme 5, eq 3). Thus, it is easy to conclude that the presence of nitrogen in the pyridine and pyrimidine ring is critical.

In the process of photoinduced cyclization of diarylethenes, the [1,5]-hydrogen shift intermediates, *cis*-4a,10a-dihydrophe-

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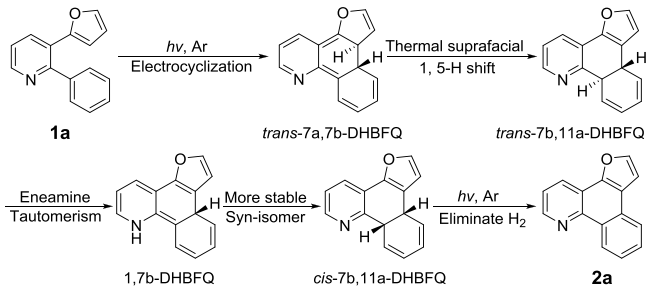
nanthrene derivatives, are rare[16] and very little is known about the nature of these photochemically generated intermediates due to their short lifetime and poor stability. In this work, on the basis of our experimental results and previous work, a detailed mechanism for the formation of dehydrogenative annulation products was proposed and presented in Scheme 6. It is believed

Scheme 6. Plausible Reaction Mechanism



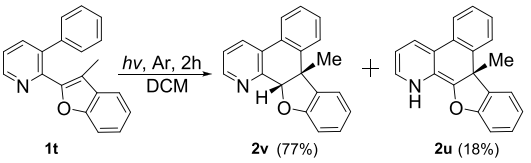
that irradiation of **1a** with a high-pressure mercury lamp led to the formation of intermediate *trans*-7a,7b-dihydrobenzo[*h*]-furo[2,3-*f*]quinoline (*trans*-7a,7b-DHBFQ) via 6π-electrocyclization, which is the first step, a typical well-known cyclization for diarylethenes.[16,17] Second, *trans*-7b,11a-dihydrobenzo[*h*]furo-[2,3-*f*]quinoline (*trans*-7b,11a-DHBFQ) was formed via a suprafacial [1,5]-H shift, driven by the rearomatization of the furan ring. The process of the [1,5]-H shift has been successfully validated by the irradiation of **1s** with further isolation and characterization of *trans*-8b,13a-DHBBQ **2s** (Scheme 5 eq 2). Third, the 1,3-eneamine tautomerization of *trans*-7b,11*a*-DHBFQ led to the formation of 1,7b-dihydrobenzo[*h*]furo-[2,3-*f*]quinoline (1,7b-DHBFQ) and then was quickly converted to the more stable *cis*-7b,11*a*-DHBFQ.

It is noteworthy to restate that the stable *cis*-isomers **6j** and **2t** have been successfully isolated and identified under the developed condition (Scheme 5, eqs 1 and 2). Moreover, due to lack of eneamine tautomerization for **9a**, no dehydrogenative annulation product **10a** was detected (Scheme 5, eq 3), which supports the eneamine tautomerization step in the proposed mechanism.

With the restoration of aromaticity for the benzene ring and formation of the entire conjugated system, the annulation product **2a** was obtained by the evolution of a hydrogen molecule (H_2) from intermediate *cis*-7b,11*a*-DHBFQ. This step has been further validated by the transformation of *cis*-8b,13*a*-DHBBI **6j** to **6i** (Scheme 5, eq 1). Moreover, the H_2 byproduct was also successfully detected by gas chromatography during the irradiation of 4-(3-(furan-2-yl)pyridin-2-yl)benzonitrile **1h** in a quartz tube (Scheme 5, eq 4; results are shown in the Supporting Information). As the annulation condition does not require any transition metals, oxidants, and other additives, compared to the literature reports,[7−11] we believe that the photoinduced intermolecular annulation of *o*-phenylfuran-2-ylpyridines and their analogues proceeds via an acceptorless dehydrogenative process.

To further validate the proposed acceptorless dehydrogenative annulation mechanism, 2-(3-methylbenzofuran-2-yl)-3-phenylpyridine **1t** was subjected to the optimal condition. As it is much more difficult to eliminate a molecule of methane, *cis*-8*b*-methyl-8*b*,13*a*-dihydrobenzo[*f*]benzofuro[3,2-*h*]quinoline (**2v**) was isolated in 77% yield along with the enamine tautomeric product **2u** in 18% yield (total yield of 95%, Scheme 7). Moreover, the structure of **2v** has been elucidated by single-crystal X-ray diffraction.

Scheme 7. Synthesis of 2v with a *cis*-Geometry via Photoinduced Rearrangement of 1t



In summary, the strategy for the synthesis of benzofurano/thienoquinolines, isoquinolines, and quinazolines by irradiation of *o*-phenylfuranyl/thienylpyridines/pyrimidines in the DCM with a high-pressure mercury lamp at rt under an argon atmosphere was demonstrated. As the photoinduced direct oxidative annulation of *o*-phenylfuranylpyridine and its analogues does not require the use of transition metal catalysts and oxidants, it is believed to be an acceptorless dehydrogenative reaction. The stepwise elucidation with detailed experimental data support for each single step is reported for the first time.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03556.

Experimental procedures and detailed characterization data of all new compounds (PDF)

Accession Codes

CCDC 1911401, 1934847, and 1939728 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhangzt@snnu.edu.cn.

ORCID

Jinming Fan: 0000-0001-5187-4136
Tao Wang: 0000-0002-1494-5297
Wei-Liang Duan: 0000-0003-2791-1931
Yong Liang: 0000-0002-7225-7062
Zunting Zhang: 0000-0003-0806-2452

Present Address

‡Department of Molecular Medicine, Beckman Research Institute of City of Hope, Duarte, California 91010, United States.

Author Contributions

†J.F. and W.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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