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Theoretical Investigation on Iodine-Catalyzed Aerobic Oxidation of 2-Picolyl Ketone With 1,2-Diaminobenzene in Synthesis of Quinoxaline

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Abstract

The first theoretical investigation was provided by our DFT calculation on I2-catalyzed aerobic oxidation of 2-picolyl ketone leading to 1,2-dicarbonyl compound with 1,2-diaminobenzene. Initially, the 2-picolyl ketone is coordinated with molecular iodine to realize iodination. Promoted by base, one hydrogen iodide is assembled and cleaved producing an N-iodo species. Then, the homolytic cleavage of N–I bond gives C-centered radical, which is bonded with additional molecular oxygen forming peroxide radical. Subsequently, a second C-centered radical couples with peroxide radical yielding peroxide dimer, which undergoes homolytic O–O bond cleavage giving two oxy-radical. After removal of second hydrogen iodide, the reaction of iodine radical I• with oxy-radical forms 1,2-dicarbonyl compound. Via three steps of condensation between 1,2-diaminobenzene and 1,2-dicarbonyl compound, the product quinoxaline is finally yielded. The condensation in last step is rate-limiting for I_2-catalyzed aerobic oxidation of 2-picolyl ketone with 1,2-diaminobenzene to quinoxaline.

Keywords: Iodine, Picolyl Ketone, 1,2-Diaminobenzene, C(sp3) –H Bond, Quinoxaline

1. Introduction

As vital architecture with biological properties, pyridyl 1,2-diketones are valuable in synthesis of various N-heterocyclic compounds. For instance, Kaur realized five- and six-membered N-heterocycles from dicarbonyl compounds [1]. Mondal reported photochemical synthesis of 1, n-dicarbonyls [2]. Dwivedi explored medicinal chemistry-based analysis on pyridine-containing heterocycles [3]. Qi discovered approach to visible light-activatable bioactive triarylimidazoles [4]. Effective synthetic methods to 1,2-dicarbonyl compounds has attracted much attention including silver-catalyzed decarboxylative couplings of acids, anhydrides and functionalized iodoarene catalysis for iodine (III) oxidations [5,6]. In this field, Riley oxidation is classic through oxidation of α-methylene adjacent to carbonyl. Many achievements have been made in recent years such as SeO2-mediated oxidative transposition of pauson-khand products, lewis acid-promoted formation of benzoselenazole derivatives, serendipitous approach for synthesis of fused [1,3] dioxolo[4,5-d] [1,3] dioxoles in trifluoroacetic acid-mediated oxidative self-condensation of acetophenones and synthesis of heteroaryl 1,2-diketones [7-10].

Among systems for conversion of methyl ketone to ketoaldehyde, I2–DMSO is well-known efficient including sequential iodination and Kornblum oxidation. Recently, Wang reported C–C and C– heteroatom bonds formation mediated by I2/DMSO catalytic system [11]. Acharya developed C(sp3) –H functionalization of methyl-azaarene through kornblum oxidation in iodine–DMSO catalysis [12]. Tang researched self-organized network for cascade reaction [13]. Wang summarized advances in self-organized total synthesis of natural products [14]. What's more, 1,2-dicarbonyl compounds can be obtained through alcohol oxidation [15,16]. or via unsaturated hydrocarbon [17,18]. 2-Iodoxybenzenesulfonic acid can function as catalyst in selective oxidation of alcohol to carboxylic acids, aldehydes, enones, and ketones with oxone.

The selective C(sp3) –C(sp3) bond cleavage and functionalization can be enabled by visi-ble-light-induced alkoxyl radical generation. The diaryl- and alkylarylalkyne can be converted into 1,2-diketone via ICl/AgNO3-catalyzed radical oxidation. The 1,2-diketone can be synthesized from alkyne under transition-metal free condition. There is also oxidation of 1,3-diketone in cop-per/iodine-cocatalyzed C–C cleavage and photoredox-mediated aerobic oxidative cleavage of 1,3-diketone to 1,2-diketone, (Z)-1,4-enedione [19,20].

In the field of reaction promoted by iodine (I2), Chang group has made many contributions such as synthesis of functionalized imidazolium salts via iodine-mediated annulation of enamine, 1,2-fused/disubstituted

benzimidazoles by I2-mediated sp3 C–H amination and spiroindolenine via iodine-mediated dearomative aza-spirocyclization of indole [21-23] especially recent progress of direct α-C–H amination of pyridyl carbonyl compounds [24]. Another breakthrough was iodine-catalyzed aerobic oxidation of picolyl ketones leading to 1,2-dicarbonyl compounds [25]. Although desired quinoxaline derivative was synthesized, how picolyl ketone transformed into corresponding 1,2-dicarbonyl compounds? What's the function of iodine as a Lewis acid catalyst? How detailed base-promoted iodination, homolytic cleavage of N–I bond, peroxide radical generation were realized in real reaction path? To solve these problems puzzled in experiment, an in-depth theoretical study was necessary for this strategy.

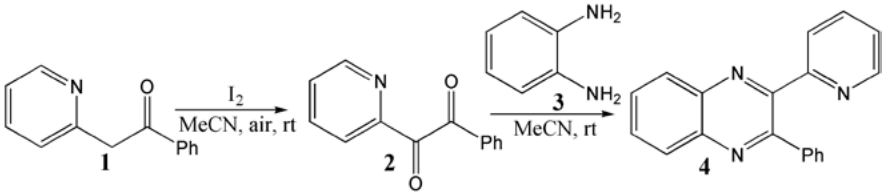
1.1. Computational Details

The geometry optimizations were performed at the B3LYP/BSI level with the Gaussian 09 package [26,27]. The mixed basis set of LanL2DZ for Fe and 6-31G(d) for other non-metal atoms [28-32] was denoted as BSI. Different singlet and multiplet states were clarified with B3LYP and ROB3LYP approaches including Becke's three-parameter hybrid functional combined with Lee–Yang–Parr correction for correlation [33,34]. The nature of each structure was verified by performing harmonic vibrational frequency calculations. Intrinsic reaction coordinate (IRC) calculations were examined to confirm the right connections among key transition-states and corresponding reactants and products. Harmonic frequency calculations were carried out at the B3LYP/BSI level to gain zero-point vibrational energy (ZPVE) and thermodynamic corrections at 298 K and 1 atm for each structure in acetonitrile (MeCN). The solvation-corrected free energies were obtained at the B3LYP/6-311++G(d,p) (LanL2DZ for Pd) level by using integral equation formalism polarizable continuum model (IEFPCM) in Truhlar's "density" solvation model [35-37] on the B3LYP/BSI-optimized geometries.

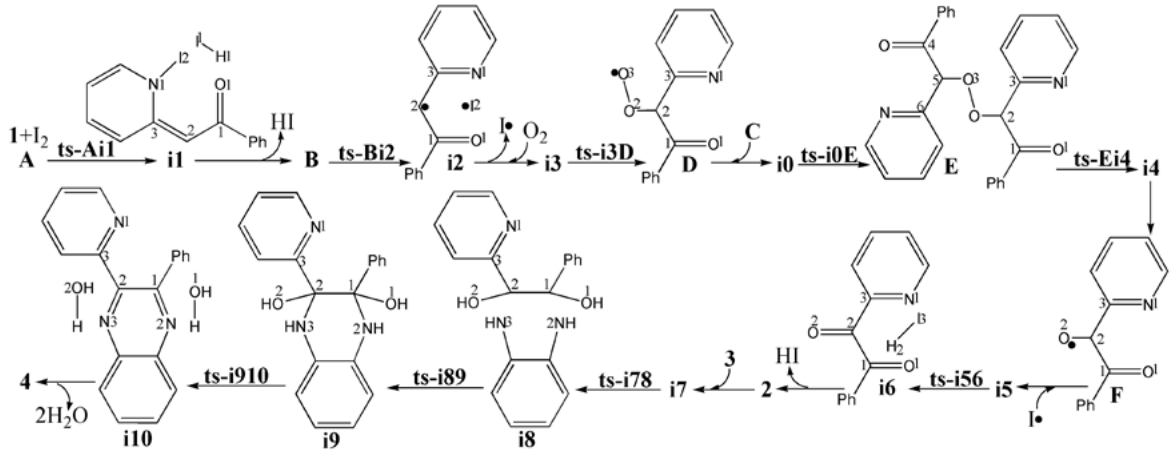
As an efficient method of obtaining bond and lone pair of a molecule from modern ab initio wave functions, NBO procedure was performed with Natural bond orbital (NBO3.1) to characterize electronic properties and bonding orbital interactions [38,39]. The wave function analysis was provided using Multiwfn_3.7_dev package including research on frontier molecular orbital (FMO) [40].

2. Results and Discussion

The mechanism was explored for I2-catalyzed aerobic oxidation of 2-picolyl ketone 1 leading to 2 with 1,2-diaminobenzene 3 in synthesis of quinoxaline 4 (Scheme 1). Shown by black arrow of Scheme 2, the substrate 2-picolyl ketone 1 is initially coordinated with molecular iodine I2 to realize iodination denoted as complex A. Under the promotion of base, one molecule of hydrogen iodide HI is assembled and cleavage from the system producing an N-iodo species B. Then, homolytic cleavage of N–I bond in B gives a C-centered radical C, which is bonded with additional molecular oxygen forming peroxide radical D. Subsequently, a second radical C couples with D yielding a peroxide dimer intermediate E, which undergoes homolytic O–O bond cleavage giving two molecules of oxy-radical F. The reaction of radical F with an iodine radical I• forms 1,2-dicarbonyl compound 2 after removal of second molecule HI. Finally, the product quinoxaline 4 is afforded via complicated condensation of 2 with 1,2-diamino-benzene 3. The schematic structures of optimized TSs are illus-trated by Figure 1 in Scheme 2. Table 1 gave activation energy for all steps.



Scheme 1 I2-catalyzed aerobic oxidation of 2-picolyl ketone **1** leading to **2** with 1,2-diaminobenzene **3** in synthesis of quinoxaline **4**.



Scheme 2 Proposed reaction mechanism of I2-catalyzed aerobic oxidation of **1** leading to **2** with **3** in synthesis of **4**.

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3.1 iodination/homolytic cleavage/peroxide radical/ radical coupling

First, the complex **A** is formed via coordination of 2-picolyl ketone **1** with one molecular iodine I2 to realize iodination. In step 1, one molecule hydrogen iodide HI is assembled via **ts-Ai1** with the activation energy of 17.3 kcal mol^{-1} exothermic slightly by -5.4 kcal mol^{-1} producing complex **i1** (black dash line of Figure 1a). Promoted by base, the cleavage of HI is easy leading to an N-iodo species **B** as another starting point of next step. The transition vector corresponds to breaking of I1•••I2, O1•••H1 and approaching of H1 to I1 (2.82, 1.27, 2.0 Å).

The conjugated structure of **B** enables the homolytic cleavage of N−I bond readily accessible. Thus in step 2, the process proceeds with a low barrier of 3.9 kcal mol−1 via **ts-Bi2** exothermic by -5.0 kcal mol−1 (red dash line of Figure 1a). **i2** is generated binding iodine radical I• and C2-centered radical C, the stability of which is greatly enhanced than the initial case with single electron located on N1. The transition vector is simple about rupture of N1•••I2 single bond (2.69 Å) (Figure S1a).

Then C and additional molecular oxygen forms intermediate **i3**, from which the attack of C2 to O2 happens with mediate activation energy of 14.1 kcal mol−1 via **ts-i3D** in step 3 delivering peroxide radical **D** with huge heat release of -47.6 kcal mol−1 (blue dash line of Figure 1a). From transition vector, the detailed atomic motion not only includes closing of C2 to O2 but the stretching of O2•••O3 to single one. The complex D is rather stable with single electron shifting from C2 to terminal O3.

With two highly reactive C-centered radical **C** and peroxide radical **D** in hand, the following step 4 takes place from initial intermediate **i0** via **ts-i0E** with activation energy of 11.1 kcal mol−1 continuously exothermic by -12.3 kcal mol−1 affording peroxide dimer intermediate **E** (magenta dash line of Figure 1a). Evidently, the coupling between **C** and **D** is favorable seen from the transition vector of radical C5•, O3• bonding as single one (2.18 Å). Furthermore, the subsequent homolytic cleavage at O−O bond from **E** in step 5 turns to be more easily with a low barrier of 6.0 kcal mol^{-1} via **ts-Ei4** exothermic by -11.0 kcal mol^{-1} giving intermediate **i4** binding two molecules of oxy-radical **F**. The transition vector contains elongation of O2•••O3 to breaking down (1.48 Å). Hence, under the assistance of I2, the five steps just mentioned are all exothermic with moderate to low barriers readily accessible both from thermodynamics and kinetics. This confirms the function of catalyst I2.

TS	$\Delta G^{\neq}_{gas}$	$\Delta G^{\neq}_{sol}$
ts-Ai1	18.7	17.3
ts-Bi2	4.6	3.9
ts-i3D	19.2	14.1
ts-i0E	13.4	11.1
ts-Ei4	5.5	6.0
ts-i56	28.9	24.5
ts-i78	24.0	23.1
ts-i89	30.9	28.7
ts-i910	32.2	30.1

Table 1 Activation energy (in kcal mol^{-1}) in gas and solvent

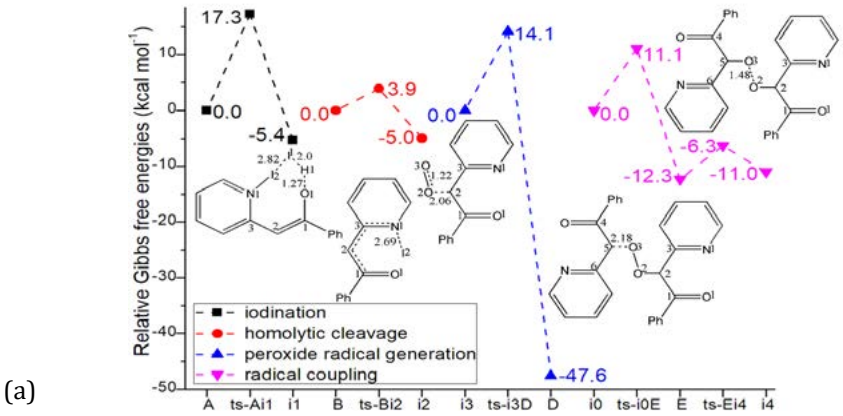
Table S1. Calculated relative energies (all in kcal mol -1 , relative to isolated species) for the ZPE-corrected Gibbs free energies (ΔG gas), Gibbs free energies for all species in solution phase (ΔG sol) at 298 K by B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) method and difference between absolute energy.

Species	ΔG_{gas}	ΔG_{sol}(EtOH)
1+i2	0.00	0.00
A	-149.39	-140.26
ts-Ai1	-130.71	-122.95
i1	-152.11	-145.63
1+i2-hi	0.00	0.00
B	-124.69	-118.52
ts-Bi2	-120.06	-114.57
i2	-131.04	-123.50
1+i-hi	0.00	0.00
C	18.45	16.01
1+i-hi+o2	0.00	0.00

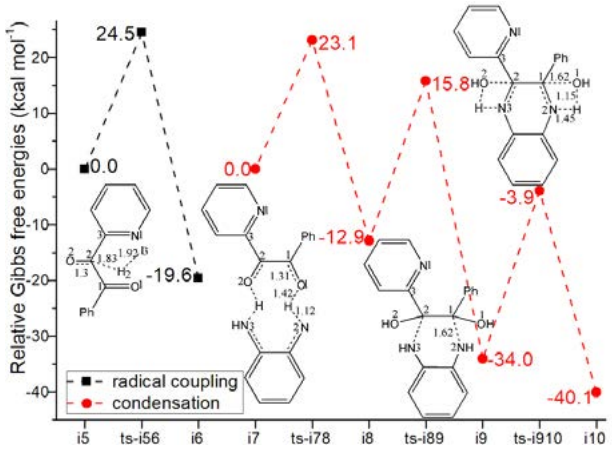
i3	34.89	34.95
ts-i3D	54.08	49.06
D	-2.73	-12.60
D+C	0.00	0.00
i0	-46.35	-52.39
ts-i0E	-32.96	-41.34
E	-64.89	-64.71
ts-Ei4	-59.38	-58.69
i4	-63.00	-63.43
(D+C)/2	0.00	0.00
F	-11.78	-16.23
(D+C)/2+i	0.00	0.00
i5	-235.53	-222.18
ts-i56	-206.68	-197.68
i6	-255.30	-241.80
(D+C)/2+i-hi	0.00	0.00
2	-70.07	-61.05
2+3	0.00	0.00
i7	11.02	17.06
ts-i78	35.03	40.17
i8	2.24	4.17
ts-i89	33.10	32.86
i9	-18.85	-16.97
ts-i910	13.39	13.17
i10	-25.91	-23.04
2+3-2h2o	0.00	0.00
4	-9.64	-15.64

Table S2. The activation energy (local barrier) (in kcal mol^{-1}) of all reactions in the gas, solution phase calculated with B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) method.

TS	$\Delta G\neq_{gas}$	$\Delta G\neq_{sol}$
ts-**Ai1** (518i)	18.7	17.3
ts-**Bi2** (94i)	4.6	3.9
ts-**i3D** (473i)	19.2	14.1
ts-**i0E** (101i)	13.4	11.1
ts-**Ei4** (47i)	5.5	6.0
ts-**i56** (363i)	28.9	24.5
ts-**i78** (714i)	24.0	23.1
ts-**i89** (1417i)	30.9	28.7
ts-**i910** (2157i)	32.2	30.1



(a)



(b)

Figure. 1 Relative Gibbs free energy profile in solvent starting from complex (a) **A, B, i3, i0** (b) **i5, i7** (Bond lengths of optimized TSs in Å).

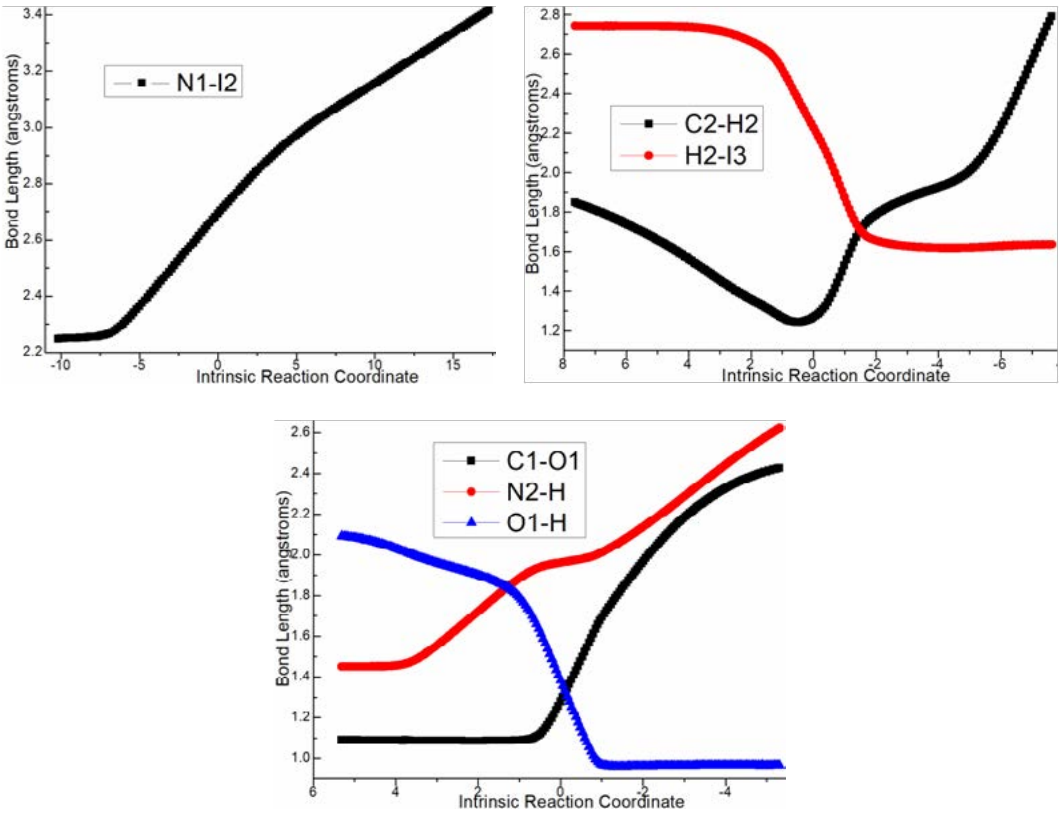


Figure S1. Evolution of bond lengths along the IRC for (a) ts-**bi2** (b) ts-**i56** (c) ts-**i910** at B3LYP/6-311++G(d,p) level.

3.2 oxy-iodine radical coupling/condensation of 2 with 3

In step 6, an intermediate **i5** is firstly assembled between radical **F** and an iodine radical I•. The coupling reaction occurs with increased activation energy of 24.5 kcal mol^{-1} via **ts-i56** exothermic by -19.6 kcal mol−1 giving intermediate **i6**. Seen from the transition vector (Figure S1b), the single electron transferring from terminal O2 to H2 on C2 not only makes C2=O2 as new double bond but forms the second molecule HI. Thereby 1,2-dicarbonyl compound **2** is obtained after removal of HI. Detailed atomic motion involves H2 leaving from C2 to I3 and shortening of C2•••O2 to double one (1.83, 1.92, 1.3 Å). **i6** is stable due to disappearance of radical.

The product quinoxaline **4** is proposed to yield via condensation of **2** with 1,2-diamino-benzene **3** in following three steps. Via **ts-i78** in step 7, hydrogen on amino group transfers to carbonyl oxygen realizing hydroxyl. The activation energy is 23.1 kcal mol^{-1} exothermic by -12.9 kcal mol−1. The transition vector contains breaking of N2•••H, bonding of O1•••H and stretching of C1•••O1 to single one (1.12, 1.42, 1.31 Å). Here C1 and C2 of resultant **i8** is positive easy to be nucleophilic attack ready for next step. Then in step 8 via **ts-i89** with activation energy of 28.7 kcal mol^{-1} exothermic by -34.0 kcal mol^{-1}, **i8** undergoes nucleophilic addition of N2 to C1 accomplishing closure of six-membered ring in intermediate **i9**. The transition vector comprises N2•••C1 approach and sp3 hybrid C1, C2 (1.62 Å). At last, the hydroxyl on C1 and H on N2 forms new water via **ts-i910** in step 9 with activation energy of 30.1 kcal mol^{-1} slightly high exothermic by -40.1 kcal mol^{-1}. From final intermediate **i10**, the elimination of two H2O makes new C1=N2 and C2=N3 double bond for product **4**. The transition vector reveals breaking of O1H from C1, H from N2 and concerted H•••O1H connection (1.45, 1.62, 1.15 Å) (Figure S1c). Comparatively, the condensation in final step 9 is determined to be rate-limiting for I2-catalyzed aerobic oxidation of 2-picolyl ketone with 1,2-diaminobenzene to quinoxaline.

4 Conclusions

The first theoretical investigation was provided by our DFT calculation on I2-catalyzed aerobic oxidation of 2-picolyl ketone leading to 1,2-dicarbonyl compound with 1,2-diaminobenzene. Initially, the substrate 2-picolyl ketone is coordinated with molecular iodine I2 to realize iodination. Promoted by base, one hydrogen iodide HI molecule is assembled and cleaved from the system producing an N-iodo species. Then, homolytic cleavage of N–I bond gives C-centered radical, which is bonded with additional molecular oxygen O2 forming peroxide radical. Subsequently, a second C-centered radical couples with peroxide radical yielding peroxide dimer intermediate, which undergoes homolytic O–O bond cleavage giving two oxy-radical molecules. The reaction of iodine radical I• with oxy-radical forms 1,2-dicarbonyl compound after removal of second HI molecule. The product quinoxaline is finally yielded via three steps of condensation between 1,2-dicarbonyl compound and 1,2-diaminobenzene. The condensation in last step is determined to be rate-limiting for I2-catalyzed aerobic oxidation of 2-picolyl ketone with 1,2-diaminobenzene to quinoxaline.

Electronic Supplementary Material

Supplementary data available: [Computation information and cartesian coordinates of stationary points; Calculated relative energies for the ZPE-corrected Gibbs free energies (ΔGgas), and Gibbs free energies (ΔGsol) for all species in solution phase at 298 K.]

Author contributions: Conceptualization, Nan Lu; Methodology, Nan Lu; Software, Nan Lu; Vali-dation, Nan Lu; Formal Analysis, Nan Lu; Investigation, Nan Lu; Resources, Nan Lu; Data Curation, Nan Lu; Writing-Original Draft Preparation, Nan Lu; Writing-Review & Editing, Nan Lu; Visuali-zation, Nan Lu; Supervision, Nan Lu; Project Administration, Nan Lu. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest: The authors declare no conflict of interest.

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