Light-triggered elimination of CO₂ and absorption of O₂ (artificial breathing reaction) in photolysis of 2-(4-nitrophenyl)-1*H*-indole derivatives

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Abstract

A new chromophore, 2-(4-nitrophenyl)-1*H*-indole (NPI), was synthesized as a potential photolabile protecting group. Caged benzoic acids featuring the NPI chromophore were synthesized as model compounds. Benzoic acid was released in moderate yields (~40–60%) upon photolysis of the caged benzoic acids without any additional chemical reagents. Interestingly, an aldehyde, 1-(5-(1-formyl-1*H*-indol-2-yl)-2-nitrophenyl)ethyl benzoate, was isolated in ~20% together with benzoic acid (~40%) in photolysis of a caged benzoic acid, 2-(2-(3-(1-(benzoyloxy)ethyl)-4-nitrophenyl)-1*H*-indol-1-yl)acetic acid. The functional group, CH₂COOH, at the indole nitrogen was transformed into the aldehyde group, CHO, under photolysis conditions in air. The similar photochemical transformation was observed in the photolysis of 2-(2-(4-nitrophenyl)-1*H*-indol-1-yl)acetic acid, in which the benzoate group is not attached at the nitrophenyl ring. Products analysis, transient absorption spectroscopy, and computational study suggested that intramolecular electron transfer is key for the elimination of CO₂ and absorption of O₂ for the formation of the aldehyde. The artificial breathing-type reaction can apply to transition metal-free oxidation of amino acids under mild conditions.

Graphic abstract

Keywords Indoles · Photochemical decarboxylation · Electron transfer · Laser flash photolysis

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1 Introduction

The “caging and uncaging” of bioactive compounds involve the temporal masking (caging) with a photoremovable protecting group (PPG) and the subsequent unmasking (uncaging) by photolysis, which is an useful strategy to investigate biochemical processes and their mechanisms [1–12]. Several types of PPGs have been developed since 1962 [13–20]. In particular, *o*-nitrophenyl-type chromophores have been widely applied in neurobiology and biomedicines (Fig. 1a) [21–25].

We have been developing a series of new PPGs based on the cyclic stilbene scaffold [6]. For example, the *p*-nitrophenyl benzofuran (NPBF) chromophore was synthesized and explored as a potential two-photon responsive PPG for Ca^{2+} -mediated uncaging (Fig. 1) [26–28]. In this study, we designed the related *p*-nitrophenyl indole (NPI) chromophore featuring the electron-donating character of the indole nitrogen atom and a polar group ($\text{CH}_2\text{CO}_2\text{H}$), which may increase the water solubility, at the nitrogen atom [29].

Compounds **1** and **2**, which are the caged benzoic acid equivalents, were synthesized and their photochemical reactions were investigated in detail. Interestingly, upon photolysis of **2** under air, in addition to the expected release of benzoic acid, we observed an efficient transformation of the “ $\text{R}=\text{CH}_2\text{CO}_2\text{H}$ ” group to the “ $\text{R}=\text{CHO}$ ” moiety. To understand the generality and mechanism of this interesting

reaction, **3** and **4** were synthesized and their photolysis was conducted under similar conditions. Further, we employed transient absorption spectroscopy and computational studies to understand the novel chemical transformation.

2 Results and discussion

2.1 Synthesis of compounds 1–4

The synthesis of compounds **1–4** is shown in Scheme 1. The selective nitration of bromide **5** afforded compound **6** in 60%, followed by the reduction of the ketone moiety produced alcohol **7** in 95% (Scheme 1a). The Suzuki–Miyaura coupling with indole derivative **9** gave 2-(4-nitrophenyl) indole **10** in 90%. The condensation with benzoic acid (**11**) gave compound **1** in 95%. A polar substituent, $\text{CH}_2\text{CO}_2\text{H}$, was introduced at the nitrogen atom using *t*-butyl bromoacetate to afford compound **2** via compound **12** in 86% in two steps from **1**. The synthesis of compound **3** was achieved by Suzuki–Miyaura coupling of compound **13** with compound **9**, and followed by the introduction of $\text{CH}_2\text{CO}_2\text{H}$ group (Scheme 1b). Compound **4** was synthesized by the N-methylation of compound **14** in 81%. The molecular structures were confirmed by ^1H NMR, ^{13}C NMR, and ESI–MS (experimental section, Figures S1–26).

Fig. 1 **a** *o*-Nitrophenyl chromophore for uncaging reaction of X; **b** *p*-Nitrophenyl benzofuran chromophore (NPBF) and 2-(4-nitrophenyl)-1*H*-indole (NPI) derivatives

Scheme 1 Reagents and conditions: **a** KNO_3 , H_2SO_4 , 0°C to RT, 2 h, 60%. **b** NaBH_4 , MeOH, 0°C to RT, 1 h, 95%. **c** (1,5-Cyclooctadiene) (methoxy)iridium dimer, 4,4'-di-tert-butyl-2,2'-bipyridine, bis (pinacolato) diboron, RT, 18 h, 90%. **d** $\text{Pd}(\text{PPh}_3)_4$, K_2CO_3 , THF/ H_2O , reflux, 15 h, 88%. **e** Benzoic acid (**11**), DMAP, DCC, CH_2Cl_2 , RT, 16 h, 95%. **f** *t*-butyl bromoacetate, KI, K_2CO_3 , MeCN, RT, 12 h, 95%. **g** TFA, CH_2Cl_2 , RT, 12 h, 91%. **h** $\text{Pd}(\text{PPh}_3)_4$, K_2CO_3 , THF/ H_2O , reflux, 15 h, 81%. **i** *t*-butyl bromoacetate, KI, K_2CO_3 , MeCN, RT, 12 h, 68%. **j** TFA, CH_2Cl_2 , RT, 12 h, 9%. **k** Iodomethane, KOH, MeCN, RT, 3 h, 72%

2.2 Photophysical property of compounds 1–4

Table 1 summarizes the photophysical properties, i.e., absorption maximum (λ_{max}), molar absorption coefficient (ϵ), fluorescence 0–0 band ($\lambda_{\text{f0-0}}$), phosphorescence 0–0 bands ($\lambda_{\text{p0-0}}$), quantum yield of fluorescence (Φ_{f}), fluorescence lifetime (τ), fluorescence rate constant (k_{f}), and the maximum of intersystem crossing (ISC) rate constant (k_{ISC}) of **1–4** in 2-methyltetrahydrofuran (2-MeTHF). The absorption and emission spectra in polar solvents are shown in the Supporting Information (SI). The relatively large Stokes shift (~ 200 nm) and solvent effect on the emission maxima of **1–4** suggest that the emission is originated from their charge-transfer state [30, 31]. Indeed, the fluorescence maxima of **1–4** in DMSO were bathochromically shifted by ~ 90 nm compared to those in 2-MeTHF (Figure S27–31). Accordingly, the charge-transfer character renders small energy gaps ($\Delta E_{\text{ST}} = E_{\text{S1}} - E_{\text{T1}}$) of the excited singlet (λ_{f00}) and triplet states (λ_{p00}) of **1–4** [32, 33], which would lead to a smooth ISC and causes weak fluorescence (Table 1). The nitro group would also accelerate the ISC process [34]. Because ΔE_{ST} is small (Table 1), thermally activated delayed fluorescence of **3** was observed in the laser flash photolysis (LFP) experiments (Figure S32) [35–38].

2.3 Photochemical reaction of compounds 1–4

First, the photochemical reactions of **1** and **2** were carried out in DMSO and MeOH, respectively, at 370 ± 10 nm with a Xe-lamp under air at $\sim 25^\circ\text{C}$ (Table 2), as the solubility of **1** is poor in MeOH. The reaction progress during the irradiation of compound **1** was monitored in DMSO- d_6 by ^1H NMR spectroscopy (Figure S33). The formation of benzoic acid (**11**) was confirmed by comparison with the authentic NMR signals of **11**, and the chemical yield of the released benzoic acid was found to be 50% (entry 1 in Table 2, Figure S33). The thermally and photochemically labile nitroso compound derived from the nitrophenyl unit was not isolated. In the photolysis of **2**, benzoic acid (**11**) was isolated in 40% yield (entry 2). Interestingly, during purification of the products, an aldehyde, 1-(5-(1-formyl-1H-indol-2-yl)-2-nitrophenyl)ethyl benzoate (**16**), was isolated in 20% yield (Figure S34e, entry 2 in Table 2).

a synthesis of compounds 1 and 2

b synthesis of compounds 3 and 4

Table 1 Photophysical data for **1–4**

Entry		λ_{abs} (nm) ^a	ϵ (M ⁻¹ cm ⁻¹) ^a	$\lambda_{\text{f0-0}}$ (nm) ^a (E_{S1} /kJ mol ⁻¹)	$\lambda_{\text{p0-0}}$ (nm) ^a (E_{T1} /kJ mol ⁻¹)	Φ_{f} % ^b	τ (ns) ^a	k_{f} (10 ⁹ s ⁻¹)	k_{isc} (10 ⁹ s ⁻¹) ^c
1	1	381	15,783	453 (264)	540 (222)	7.3	0.9	1.1	14
2	2	363	13,334	472 (253)	517 (231)	2.1	0.6	1.7	78
3	3	369	16,146	440 (271)	463 (258)	3.1	1.1	0.9	28
4	4	374	21,322	452 (265)	493 (242)	2.2	0.7	0.15	66

^aAbsorbance, molar extinction coefficient, fluorescence, and fluorescence lifetime (τ) determined in 2-MeTHF at ~25 °C. Phosphorescence was measured at 77 K in 2-MeTHF. The 0–0 bands were determined from the onset of the emission spectra. E_{S1} is the energy of the singlet excited state. E_{T1} is the energy of the triplet state

^bFluorescence quantum yield (Φ_{f}) determined using 9,10-diphenylanthracene as a reference standard [39]

^cThe maximum of k_{isc} is calculated using $k_{\text{isc}} = k_{\text{f}}/\Phi_{\text{f}} - k_{\text{f}}$

Table 2 Reaction of **1** and **2** under various conditions

Entry	compound	Solvent	Reaction conditions	Benzoic acid (11)	Aldehyde 16
1	1	DMSO-d ₆	$h\nu$ (370 ± 10 nm) under air, r.t	50%	–
2	2	CD ₃ OD	$h\nu$ (370 ± 10 nm) under air, r.t	40%	20%
3	2	CD ₃ OD	$h\nu$ (370 ± 10 nm) Under N ₂	61%	Not detected
4	2	CD ₃ OD	Under dark for 1 week, under air, r.t	Not detected	Not detected
5	2	DMSO-d ₆	Heat at 100 °C for 10 h	Not detected	Not detected

Surprisingly, this indicated that the methyl carboxylic acid group (CH₂CO₂H) was transformed to the aldehyde moiety (CHO) during photolysis. The quantum yield of the photochemical decomposition of **2** was determined to be 17% by the ferrioxalate actinometer method (see, SI) and was

considerably higher than the yield (2%) of the photochemical decomposition of **1**.

To understand the mechanism of this novel chemical transformation, we carried out control experiments with **2** under photochemical and thermal conditions (entries 3–5).

Under a nitrogen atmosphere, the aldehyde was not detected in the reaction, and benzoic acid alone was isolated in 61% yield (entry 3), indicating that molecular oxygen is required for the aldehyde formation. In contrast to the photochemical behavior, **2** was stable under dark conditions in MeOH and DMSO at 100 °C (entries 4, 5). Thus, the formation of the aldehyde required both the irradiation and the presence of molecular oxygen.

Because the benzoate moiety in **2** was intact under the photolysis conditions during the formation of **16**, compound **3** without the benzoate group was synthesized to probe the photochemical behavior. The photochemical reaction of **3**

(Fig. 2) was carried out under conditions (air and 370 nm irradiation) similar to those used for the photolysis of **2**. Aldehyde **18** was formed in 11% together with **17** and **19** in 43 and 32% yield, respectively. As shown in Fig. 2b, hydroperoxide **17** (Fig. 2d) was the primary photolysis product from **3**, because a clear NMR signal at 5.9 ppm was observed after 30 min of irradiation. The other two products, aldehyde **18** (Fig. 2e) and alcohol **19** (Fig. 2f), were detected after 1 h of photolysis (Fig. 2c). The total chemical yield of the products isolated from the photolysis of **3** was over 85%. In addition to **17–19**, 2-(4-nitrophenyl)-1*H*-indole (**14**), which was not detected in the photolysate, was obtained in a small amount

Fig. 2. ^1H NMR spectroscopy analysis of **3** photolysis (18 mM) at 365 nm in CD_3OD ; **a** before irradiation; **b** after 30 min irradiation; **c** after 1 h irradiation; **d** ^1H NMR spectrum of 1-(hydroperoxymethyl)-2-(4-nitrophenyl)-1*H*-indole (**17**); **e** 2-(4-nitrophenyl)-1*H*-indole-1-carbaldehyde (**18**); **f** 2-(4-nitrophenyl)-1*H*-indol-1-yl)methanol (**19**) in CD_3OD , δ 6–9 ppm

through silica gel column chromatography of the crude products. The formation of **14** is attributed to the decomposition of alcohol **19** owing to the instability of the methanol amine under acidic conditions [40]. Results similar to such a photoreaction were also observed in different solvents such as acetonitrile (Figure S35) and DMSO (Figure S36). Because of the poor solubility of **3**, nonpolar solvents could not be used for the photoreaction. Analysis of the products of the photochemical reaction of **3** revealed that molecular oxygen (O_2) was consumed, and carbon dioxide (CO_2) was eliminated during the photolysis, in a phenomenon reminiscent of “breathing”. In contrast to the high photoreactivity of **3**, compound **4** remained intact after 1-h irradiation at 365 nm in DMSO at rt.

2.4 Transient absorption spectroscopy of compounds **3** and **4**

To gain more insights into the reaction mechanism of the breathing-type phenomenon, we employed transient

absorption (TA) spectroscopy at sub-nanosecond and sub-microsecond time scales using the randomly interleaved pulse train (RIPT) method [41] for the photolysis of **3** and **4**. The TA spectrum observed in the photolysis of **3** looks similar to that obtained in the photolysis of **4** (Fig. 3a, c). However, the significant difference was found by the careful analysis of the wavelength dependence of their time profiles (Fig. 3b, d).

Figure 3a shows the TA spectra of **3** in the Ar-saturated acetonitrile solution using a 355 nm laser (25 ps pulse, 80 μ J). The absorption maxima were observed at around 600 and 800 nm immediately after the flash photolysis. However, the maximum shifted to $\sim$ 820 nm after 700 ns (Fig. 3a), indicating that at least two transient species are generated in the photolysis of **3**. The decay rate constants at 620 and 820 nm were determined to be $2.0 \times 10^6 \text{ s}^{-1}$ (blue, 500 ns at 620 nm) and $1.3 \times 10^6 \text{ s}^{-1}$ (orange, 770 ns at 820 nm), respectively (Fig. 3b). Thus, a transient at 820 nm decayed more slowly than that at 620 nm. The significant quenching of the decay rate constants was observed under air

Fig. 3 TA spectra observed after the 355 nm laser irradiation (25 ps pulse, 80 μ J). **a** photolysis of **3** (8.5×10^{-5} M) and **c** photolysis of **4** (1.0×10^{-4} M) in acetonitrile under argon (Ar) atmosphere at 298 K. The kinetic traces for **(b)** **3** and **(d)** **4** in the nanosecond time region

($[O_2] = 1.9 \times 10^{-3} \text{ M}$) [42], $k_d = 4.6 \times 10^6 \text{ s}^{-1}$ (gray, 217 ns at 620 nm) and $4.4 \times 10^6 \text{ s}^{-1}$ (yellow, 227 ns at 820 nm), respectively (Fig. 3b). The decay constants under air were twice larger than those under the degassed conditions, from which the oxygen quenching rate constants at 620 and 820 nm were determined to be 1.37×10^9 and $1.63 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, respectively. The fast-quenching rate constants support that these signals are paramagnetic species.

A similar TA spectrum with ~600 and ~800 nm bands was observed after the flash photolysis of compound **4** under the similar conditions for **3** (Fig. 3c). The corresponding kinetic decay traces at 620 and 820 nm are summarized in Fig. 3d. In contrast to the rate constants observed for the photolysis of **3**, in which dual decay was observed, the fall rate constants at 620 (blue in Fig. 3d) and 820 nm (orange in Fig. 3d) were both single exponentials and were determined to be $\sim 2.0 \times 10^6 \text{ s}^{-1}$ (~500 ns). Under air conditions ($[O_2] = 1.9 \times 10^{-3} \text{ M}$), the quenching of the signals was observed to obtain the decay rate constants of $4.9 \times 10^6 \text{ s}^{-1}$ (204 ns) at 620 nm and $4.7 \times 10^6 \text{ s}^{-1}$ (213 ns) at 820 nm (Fig. 3d), from which the oxygen quenching rate constant was determined to be $1.47 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. Thus, the TA spectrum in the photolysis of **4** is also assigned to a paramagnetic species. Since compound **4** was quantitatively recovered after the photolysis, the TA spectrum observed in Fig. 3c can be assigned to the T–T absorption of the triplet excited state of **4**.

2.5 Mechanism of photo-induced breathing reaction

A plausible mechanism for the photo-induced breathing-type reaction of **3** is shown in Scheme 2. Compound **3** undergoes excitation to its electronically excited state upon exposure to light and undergoes intramolecular electron transfer (ET) to generate the ammonium intermediate **20**. The electron transfer process would be accelerated by the zwitterionic form **ZI** of the amino acid moiety in **3** because compound **15**, in which the *t*-Bu group protects the carboxylic acid, was intact under the photolysis conditions. The elimination of CO_2 produces the intermediate **21**. The radical intermediate **21** is then trapped by O_2 to afford hydroperoxide **17**. As the photoreactivity of hydroperoxides is well known [43–45], **17** undergoes O–O bond scission to produce aldehyde **18** and alcohol **19** via **22**. The similar decarboxylation and generation of alkyl radicals have been reported in intermolecular photo-induced electron transfer reactions of carboxylic acids [46–55].

As mentioned in the TA spectroscopy analysis of compound **3**, two paramagnetic species were identified at ~600 nm and ~800 nm (Fig. 3a, b). One transient species was detected for compound **4** (Fig. 3c, d). The transient species is also proposed to be paramagnetic because the very

fast oxygen quenching reactions was observed. To understand the results from the time-resolved spectroscopy, first, the UV–vis spectra in acetonitrile were computed for the triplet states of **3** and **4** at the TD-UB3LYP/6-31G(d) level of theory using SMD model for the solvation (Figs. 4a,b). The triplet **3** was predicted to possess the electronic transitions mainly at 343 nm ($f=0.15$), 526 nm ($f=0.59$), and 735 nm ($f=0.18$) (Fig. 4a), which are fit to the TA spectrum in Fig. 3a under Ar just after the laser flash of compound **3**. The transitions at 521 nm ($f=0.53$) and 721 nm ($f=0.21$) were found for the triplet state of compound **4** (Fig. 4b), which reproduces well the TA spectrum observed in the laser flash photolysis of compound **4** (Fig. 3c).

Next, we conducted quantum chemical computations for the possible paramagnetic intermediates **20**, **21**, **23**, and **24** in the photo-induced breathing reaction of **3**. Those intermediates were found as equilibrium structures in the triplet states for **20,21** and doublet states for **23,24** at the UB3LYP/6-31G(d) level of theory. The UV–Vis spectra in acetonitrile were computed at the TD-B3LYP/6-31G(d) level of theory (Figs. 4c–f). Three main excitations, 359 nm ($f=0.32$), 621 nm ($f=0.19$), 752 nm ($f=0.23$), were found in the triplet state of **20** (Fig. 4c). One excitation band at 765 nm with $f=0.30$ was computed in the visible region for the triplet state of **21** at the same level of theory (Fig. 4d). No strong absorption bands were computed in the visible region for compounds **23** (422 nm, $f=0.39$, Fig. 4e) and **24** (384 nm, $f=0.168$, Fig. 4f). As judged by the computed absorption spectra, a transient species at ~820 nm in the TA analysis of compound **3** is proposed to be assigned to compound **21**. Because the computed ϵ value for the triplet state of **3** was 34,000 (Fig. 4a), which was much larger than that of **21** ($\epsilon = 12,000$, Fig. 4d), the T–T absorption spectrum of **3** dominates the TA spectrum in the photolysis compound **3** (Fig. 3a). The weak absorption spectrum of **21** is overlapped with that of triplet **3**. Furthermore, the CO_2 elimination process from **20** to **21** was computed at the UB3LYP/6-31G(d) level of theory (Scheme 2). The relatively small energy barrier, 14.8 kcal mol $^{-1}$, was found to the CO_2 elimination process. Thus, the smooth elimination of CO_2 is expected from intermediate **20**.

3 Conclusions

In summary, a new photolabile protecting group, 2-(4-nitrophenyl)-1*H*-indole (NPI), was synthesized in this study. Caged benzoic acids were prepared, and their photochemical reactions were examined. Benzoic acid was released in a moderate chemical yield of 40–60%. In addition to the formation of benzoic acid, an unexpected aldehyde was isolated during product analysis. The identification of the aldehyde product prompted us to investigate

Scheme 2 Proposed mechanism for the breathing reaction in the photolysis of **3**

Fig. 4 Computationally predicted UV-Vis spectrum at TD-B3LYP/6-31G(d) level of theory in acetonitrile: **a** triplet state of **3**, **b** triplet state of **4**, **c** triplet state of **20**, **d** triplet state of **21**, **e** doublet state

of **23**, **f** doublet state of **24**. The red bars are computed values of the electronic transitions at the TD-UB3LYP/6-31G(d) level of theory in acetonitrile using SMD model for the solvation

the mechanism of the transformation and the excited-state dynamics. Based on the TA spectroscopy and TD-DFT computational results, the intramolecular electron transfer to the excited state was proposed for the initial step of the chemical transformation to generate the zwitterion intermediate. The successive CO_2 elimination and absorption

of O_2 (breathing reaction) produced the hydroperoxide together with its photo-induced decomposition products, the alcohol and aldehyde. The photo-induced breathing-type reaction may apply to transition metal-free oxidation of amino acids.

4 Experimental section

4.1 1-(5-Bromo-2-nitrophenyl)ethan-1-one (6)

A flask was charged with KNO_3 (0.28 g, 2.76 mmol) and was cooled to 0 °C, to which H_2SO_4 (5 mL) was added slowly and mixture allowed to stir for 10 min. 3-bromoacetophenone **5** (0.50 g, 2.51 mmol) was added at 0 °C. Temperature was raised to room temperature and stirred for 2 h. Subsequently the reaction mixture was poured into crushed ice. Aqueous layer was extracted with CH_2Cl_2 . Organic layer was washed with brine, dried over Na_2SO_4 , and purified through silica gel column chromatography to give required product (365.4 mg, 60%) [26]. ^1H NMR (400 MHz, CDCl_3): δ 8.00 (d, J = 8.7 Hz, 1 H), 7.73 (dd, J = 8.7 and 2.1 Hz, 1H), 7.54 (d, J = 2.1 Hz, 1 H), 2.55 (s, 3H).

4.2 1-(5-Bromo-2-nitrophenyl)ethan-1-ol (7)

To a stirred solution of 1-(5-bromo-2-nitrophenyl)ethan-1-one **6** (2.7 g, 0.011 mol) in methanol (30 mL) was added NaBH_4 (0.45 g, 0.010 mol) in portion at 0 °C. Temperature was slowly raised to room temperature. Stirring was continued for additional 1 h. After completion of the reaction, methanol was removed under reduced pressure. Reaction mixture was partitioned between the ethyl acetate and water, organic layer was combined, washed with brine, dried over Na_2SO_4 , filtered and evaporated under reduced pressure to give the required compound which requires no further purification (2.6 g, 95%) [26]. ^1H NMR (400 MHz, CDCl_3): δ 8.03 (d, J = 2.1 Hz, 1 H), 7.82 (d, J = 8.7 Hz, 1 H), 7.55 (dd, J = 8.7 and 2.1 Hz, 1 H), 5.47 (m, 1 H), 2.24 (d, J = 3.9 Hz, 1 H), 1.57 (d, J = 1.3, 3 H).

4.3 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (9)

Inside a glove box, $[\text{Ir}(\text{cod})\text{OMe}]_2$ (6.4 mg, 0.0096 mmol), dtbpy (5.2 mg, 0.019 mmol), bis(pinacolato)diboron (162.2 mg, 0.64 mmol), the indole (150.1 mg, 1.28 mmol), and THF (2 mL) were added consecutively to a dry vial with a magnetic stir bar. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to room temperature, concentrated and purified by column chromatography to give the product. **9** (278.5 mg, 89.5%) [56], EtOAc:hexane = 1:9 (R_f = 0.3). ^1H NMR (400 MHz, CDCl_3): δ = 8.69 (br, 1 H), 7.73 (dd, J = 8 and 0.8 Hz, 1 H), 7.43 (dd, J = 8.4 and 1.2 Hz, 1 H), 7.29–7.25 (m, 1 H), 7.17–7.14 (m, 2 H), 1.42 (s, 12 H).

4.4 1-(5-(1H-Indol-2-yl)-2-nitrophenyl)ethan-1-ol (10)

To a solution of compound **9** (50.1 mg, 0.21 mmol) and **7** (50.0 mg, 0.20 mmol), K_2CO_3 (37.1 mg, 0.22 mmol) in THF/ H_2O (1:1) (2 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (11.5 mg, 0.01 mmol) under N_2 . The mixture was heated and reflux for 15 h. The reaction mixture was quenched with saturated NH_4Cl solution (6 mL) and extracted with ethyl acetate. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. Flash chromatography on silica gel using hexane/ethyl acetate afforded compound **10**. (52.4 mg, 88.4%) (EtOAc:hexane = 1:5, R_f = 0.24, then change ratio to 1:2) ^1H NMR (400 MHz, CDCl_3): δ = 8.57 (broad, 1 H), 8.15 (d, J = 1.96 Hz, 1 H), 8.08 (d, J = 8.56 Hz, 1 H), 7.71 (dd, J = 9 and 1.96 Hz, 1 H), 7.68 (d, J = 8.4 Hz, 1 H), 7.46 (d, J = 8.12 Hz, 1 H), 7.28 (t, J = 3.88 Hz, 1 H), 7.18 (t, J = 8.08 Hz, 1 H), 7.06 (d, J = 1.4 Hz, 1 H), 5.63 (q, J = 6.28 Hz, 1 H), 2.36 (broad, 1 H), 1.66 (d, J = 6.24 Hz, 3 H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 145.99, 143.94, 138.32, 137.48, 135.99, 128.88, 125.42, 124.38, 124.02, 123.24, 121.14, 120.29, 112.16, 102.16, 64.45, 25.47. mp 175–176 °C; HRMS–APCI: calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3\text{N}_2$: 283.10772, found 283.10767 $[\text{M} + \text{H}]^+$.

4.5 1-(5-(1H-Indol-2-yl)-2-nitrophenyl)ethyl benzoate (1)

Benzoic acid (13.2 mg, 0.11 mmol), DMAP (1.3 mg, 0.01 mmol) and compound **10** (28.3 mg, 0.1 mmol) in anhydrous dichloromethane (5 mL) was stirred for 10 min. To the reaction mixture DCC (20.6 mg, 0.1 mmol) was added and stirred for 16 h at room temperature. Subsequently, water was added into reaction mixture and compound was extracted with dichloromethane. The organic layer was washed with sodium bicarbonate solution and water. Dried with anhydrous sodium sulfate and evaporated under reduced pressure. Flash chromatography on silica gel afforded compound **1** (38.4 mg, 95%). Hexane:EtOAc = 5:1, R_f = 0.5. ^1H NMR (400 MHz, CDCl_3): δ = 8.44 (broad, 1 H), 8.12 (q, J = 5.44 Hz, 3H), 7.97 (d, J = 1.92 Hz, 1H), 7.61–7.69 (m, 3H), 7.51 (t, J = 7.8 Hz, 2 H), 7.42 (d, J = 7.8 Hz, 1 H), 7.25 (dd, J = 8.16 and 0.96 Hz, 1 H), 7.16 (t, J = 7.16 Hz, 1 H), 6.96 (d, J = 1.2 Hz, 1 H), 6.7 (q, J = 6.52 Hz, 1 H), 1.87 (d, J = 6.48 Hz, 3 H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 165.59, 146.32, 138.42, 138.29, 138, 135.46, 134.11, 129.79, 129.29, 128.8, 125.87, 125.47, 123.71, 123.5, 121.26, 120.4, 112.16, 102.72, 68.79, 21.72. mp 238–239 °C; HRMS–ESI: calcd for $\text{C}_{23}\text{H}_{18}\text{O}_4\text{N}_2\text{Na}$: 409.11588, found 409.11624 $[\text{M} + \text{Na}]^+$.

4.6 1-(5-(1-(2-(*tert*-Butoxy)-2-oxoethyl)-1H-indol-2-yl)-2-nitrophenyl)ethyl benzoate (**12**)

Compound **1** (39 mg, 0.1 mmol), K_2CO_3 (27.6 mg, 0.2 mmol) in 3 mL MeCN was stirred for 30 min at 60 °C oil bath. To the mixture *tert*-butyl 2-bromoacetate (39 mg, 0.2 mmol) and KI (0.87 mg, 0.005 mmol) was added and stirred 12 h. Reaction stopped and poured mixture into water extracted with EtOAc three times, washed with brine, dried with $NaSO_4$, solvent removed to get crude product. Flash chromatography on silica gel afforded pure product (54.5 mg, 95%), EtOAc:hexane = 1:4. R_f = 0.47. 1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 7.08 Hz, 2H), 7.91 (d, J = 1.76 Hz, 1H), 7.66 (d, J = 7.92 Hz, 1H), 7.57 (t, J = 9.48 Hz, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.26 (t, J = 9.9 Hz, 1H), 7.18 (t, J = 7.84 Hz, 1H), 6.7 (s, 1H), 6.67 (q, J = 6.4 Hz, 1H), 4.67 (s, 2H), 1.86 (d, J = 6.68 Hz, 3H). ^{13}C NMR (100 MHz, $DMSO-d_6$): δ 167.88, 165.53, 146.88, 139.06, 139.05, 138.82, 138.11, 133.3, 129.73, 129.69, 128.69, 128.51, 128.01, 127.74, 125.08, 123.32, 121.24, 120.98, 109.67, 104.83, 82.85, 68.65, 68.18, 47.11, 27.92, 22.23. mp 57–59 °C; HRMS–ESI: calcd for $C_{29}H_{29}O_6N_2$: 501.20201, found 501.20187 $[M+H]^+$.

4.7 2-(2-(3-(1-(Benzoyloxy)ethyl)-4-nitrophenyl)-1H-indol-1-yl)acetic acid (**2**)

Dissolved **12** (54.5 mg, 0.1 mmol) in 6 mL DCM with stirring, 2 mL TFA was added dropwise and stirred 12 h. Solvent removed to get crude product, flash chromatography on silica gel afforded pure product (40.8 mg, 91%), first EtOAc:hexane = 1:3 (R_f = 0); then change to EtOAc:MeOH: 5:1 (R_f = 0.43). 1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.48 Hz, 1H), 8.05 (dd, J = 7.08 and 1.24 Hz, 2H), 7.8 (d, J = 1.48 Hz, 1H), 7.6 (d, J = 7.76 Hz, 1H), 7.5 (t, J = 7.52 Hz, 2H), 7.4 (t, J = 7.88 Hz, 2H), 7.2–7.3 (m, 3H), 6.7 (s, 1H), 6.6 (q, J = 6.6 Hz, 1H), 4.7 (s, 2H), 1.8 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0363, 165.58, 146.92, 138.91, 138.85, 138.79, 137.68, 133.38, 129.65, 128.69, 128.53, 127.99, 127.59, 125.31, 123.53, 121.35, 121.27, 109.48, 105.12, 77.21, 68.83, 45.77, 22.11. mp 97–100 °C; HRMS–ESI: calcd for $C_{25}H_{20}O_6N_2Na$: 467.12136, found 467.12140 $[M+Na]^+$.

4.8 2-(4-Nitrophenyl)-1H-indole (**14**)

To a solution of compound **13** (1.0 g, 4.14 mmol) and **9** (1.0 g, 4.12 mmol), K_2CO_3 (74.1 mg, 0.44 mmol) in THF/ H_2O (1:1) (10 mL) was added $Pd(PPh_3)_4$ (230.2 mg, 0.2 mmol) under N_2 . The mixture was heated and reflux for 15 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The

combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. Flash chromatography on silica gel using hexane/ethyl acetate afforded compound **14**. (0.80 g, 81%) [57]. 1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1H), 8.23 (d, J = 9.04 Hz, 2H), 7.83 (d, J = 9.04 Hz, 2H), 7.69 (t, J = 7.44 Hz, 1H), 7.45 (t, J = 7.45 Hz, 1H), 7.35 (mult, 1H), 7.3 (mult, 1H), 6.96 (1H, s).

4.9 *tert*-Butyl 2-(2-(4-nitrophenyl)-1H-indol-1-yl)acetate (**15**)

Compound **14** (0.80 g, 3.34 mmol), K_2CO_3 (0.92 g, 6.68 mmol) in 30 mL ACN was stirred for 30 min at 60 °C oil bath. To the mixture *tert*-butyl 2-bromoacetate (1.3 g, 6.68 mmol) and KI (29 mg, 0.167 mmol) was added and stirred 12 h. Reaction stopped and poured mixture into water extracted with EtOAc three times, washed with brine, dried with $NaSO_4$, solvent removed to get crude product. Flash chromatography on silica gel afforded pure product (799.5 mg, 68%). 1H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, J = 9.12 Hz, 2H), 7.72 (mult, 2H), 7.31 (mult, 2H), 7.21 (mult, 1H), 6.75 (s, 1H), 4.73 (s, 2H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.84, 147.27, 139.20, 139.09, 139.01, 129.62, 128.06, 123.99, 123.40, 121.29, 121.00, 109.72, 105.04, 82.93, 47.18, 27.97. mp 118–120 °C; HRMS–ESI: calcd for $C_{20}H_{20}O_4N_2Na$: 375.13208, found 375.13156 $[M+Na]^+$.

4.10 2-(2-(4-Nitrophenyl)-1H-indol-1-yl)acetic acid (**3**)

Dissolved *tert*-butyl 2-(2-(4-nitrophenyl)-1H-indol-1-yl)acetate (536.4 mg, 1.8 mmol) in 20 mL DCM with stirring, 1 mL TFA was added dropwise and stirred 12 h. Solvent removed to get crude product, purified with GPC to get pure product (46.2 mg, 8.7%). 1H NMR (400 MHz, CD_3OD): δ = 8.36 (d, J = 8.32 Hz, 2H), 7.8 (d, J = 8.44 Hz, 2H), 7.64 (d, J = 7.96 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.27 (t, J = 7.44 Hz, 1H), 7.15 (t, J = 7.28 Hz, 1H), 6.77 (s, 1H), 4.94 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 171.10, 147.27, 139.30, 139.04, 138.95, 133.01, 129.45, 128.13, 123.49, 122.69, 122.35, 120.60, 120.30, 109.52, 104.30, 31.50. mp 172–174 °C; HRMS–ESI: calcd for $C_{16}H_{11}O_4N_2$: 295.07188, found 295.07196 $[M-H]^-$.

4.11 1-Methyl-2-(4-nitrophenyl)-1H-indole (**4**)

Dissolved 1-methyl-2-(4-nitrophenyl)-1H-indole (374.4 mg, 1.57 mmol), KOH (95.2 mg, 1.7 mmol) in 20 mL ACN and stirred for 30 min at 60 °C oil bath. Methyl iodide (392.1 mg, 2.78 mmol) was added into ACN solution and stirred 3 h. Stopped reaction and poured mixture into water, extracted

with EtOAc three times, washed with brine, dried with NaSO₄, solvent removed to get crude product. Flash chromatography on silica gel afforded pure product (283.2 mg, 72%) [58]. ¹H NMR (400 MHz, CDCl₃): δ = 8.36 (d, J = 8.8 Hz, 2H), 7.71 (t, J = 9.2 Hz, 3H), 7.43 (d, J = 4.0 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 6.74 (s, 1H), 3.83 (s, 3H).

4.12 General procedures of photoreactions of compounds 1–4

Compound **X** (X = 1–4) was dissolved in CD₃OD or DMSO-*d*₆ and transferred to NMR tube. The reaction solution was irradiated using LED lamp (365 nm). The distance between light source and sample was 10 cm. After irradiation, the solvent was removed by evaporation. The products were subjected to silica gel column chromatography to isolated products.

4.13 Time-resolved absorption spectroscopy

Subnanosecond time-resolved transient absorption spectroscopy (λ_{exc} = 355 nm, 25 ps pulse, 80 μ J) was employed to study the photolysis of compounds **3** and **4** (Abs_{355} = 0.77) in acetonitrile using a randomly interleaved pulse train (RIPT) method [41].

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Availability of data and materials Supporting information for ¹H and ¹³C NMR, emission spectra, and computational details.

Declarations

Conflict of interest There are no conflicts to declare.

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