Cascade photocaging of diazeniumdiolate: A novel strategy for one

and two photon triggered uncaging with real time reporting

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General materials and experimental techniques

All reagents were purchased from Sigma Aldrich and used without further purification. DMF and DCM were distilled from CaH₂ under nitrogen gas before use. For reaction monitoring, precoated silica gel 60 F254 TLC sheets (Merck) was used. Chromatographic purification was done with 60-120 mesh silica gel (Merck). ¹H NMR spectra were recorded on a BRUKER-AC 200, 400 and 600 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: 7.26 ppm and deuterated dimethylsulphoxide: 2.5 ppm). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz). ¹³C NMR (50, 100 and 150 MHz) spectra were recorded on a BRUKER-AC 200, 400 and 600 MHz Spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: 77.23 ppm and deuterated DMSO: 39.52 ppm). UV/vis absorption spectra were recorded on a Shimadzu UV-2450 UV/vis spectrophotometer, fluorescence emission spectra were recorded on a Hitachi F-7000 fluorescence spectrophotometer.

Photolysis was carried out using 125 W medium pressure mercury lamp, supplied by SAIC (India) using 1M CuSO₄ solution in 0.1 M H₂SO₄ as cut-off filter for transmitting light of wavelength \geq 365 nm i.e. UV light (1PE) and 730 nm laser diode (30 mW/ cm², 2 PE), supplied by coherent. HRMS spectra were recorded on a JEOL-AccuTOF JMS-T100L mass spectrometer. Imaging was done using a fluorescence microscope (IX 51, Olympus) high-performance CCD camera with the appropriate filter using Image-Pro discovery 5.1 software.

Scheme for Synthesis of ONB-COU-DEA-NONOate



(a.) CH₃I, K₂CO₃, Acetone, reflux, 17 h (b.) HNO₃, 0 °C - rt, 2 h (c.) NaBH₄, C₂H₅OH, 4 h (d.) PBr₃, dry DCM, RT, 2 h (e.) Propionic anhydride, piperidine, reflux, 6h, (f.) i) excess NBS, CCl₄, reflux, 8h ii) NaOAc, AcOH, reflux, 12h iii) 2N HCI, reflux, 30 min, RT, overnight, (g.) NaBH₄, CH₃OH, 2 h (h.) K₂CO₃, DMF, RT, 6h (i.) PBr₃, dry DMF, RT, 4 h (j.) Et₂N(N₂O₂)Na, Dry DMF, RT, 24 h

Scheme S1: Synthesis of cascade photocage ONB-COU-DEA-NONOate

Experimental procedure and Spectroscopic data

3,4-dimethoxybenzaldehyde (1)¹: Methyl iodide (0.8 mL, 12 mmol) was added to a suspension of vanillin (1.2 g, 8 mmol) and K₂CO₃ (1.1 g, 8 mmol) in acetone. The suspension was heated to reflux for 17 h and the reaction mixture was filtered, and the solids were washed with acetone. The filtrate was concentrated under reduced pressure to give compound **1** in 90% yield as pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.79 (s, 1 H), 7.40 (dd, *J* = 8 Hz, 2 Hz, 1 H), 7.34 (d, *J* = 2 Hz, 1 H), 6.92 (d, *J* = 8 Hz, 1 H), 3.90 (s, 3 H), 3.81 (s, 3 H). ¹³C NMR (150 MHz, CDCl₃) δ 190.8, 154.4, 149.5, 130.0, 126.8, 110.3, 108.9, 56.1, 55.9

4,5-dimethoxy-2-nitrobenzaldehyde $(2)^2$: Compound 1 (1.9 g, 11.5 mmol) was suspended in 12 mL of ice-cold HNO₃. The solution was slowly warmed to room temperature, and the reaction was stirred until all of the material gets dissolved. The solution was then poured onto ice and the precipitate was filtered off, followed by washing with cold water. The product was recrystallized from boiling EtOH (approximately 30 mL), affording compound 1 in 73% yield as a yellow solid. ¹H NMR (600 MHz, CDCl₃) δ 10.46 (s, 1H), 7.63 (s, 1H), 7.43 (s, 1H), 4.04 (6H). ¹³C NMR (150 MHz, CDCl₃) δ 187.76, 187.72, 153.2, 152.4, 143.9, 125.6, 109.8, 107.0, 56.8, 56.7.

(4,5-dimethoxy-2-nitrophenyl)methanol (**3**)³: To a solution of **2** (1.47 g, 7 mmol) in 200 mL of ethanol was slowly added NaBH₄ (132 mg, 3.5 mmol). The mixture was stirred at room temperature for 30 min in 0 C. The solvent was then evaporated, and the residue was partitioned between EtOAc and water. After extraction with EtOAc, the combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and evaporated and the crude product was purified by flash column chromatography (82%) as a dark orange solid. ¹H NMR (400 MHz, CDC1₃) δ 7.67 (s, 1 H), 7.17 (s, 1 H), 4.94 (s, 2 H), 3.98 (s, 3 H), 3.93 (s, 3 H). ¹³C NMR (50 MHz, CDCl₃) δ 154.1, 148.1, 139.9, 132.6, 111.1, 108.4, 62.9, 56.6

1-(bromomethyl)-4,5-dimethoxy-2-nitrobenzene (**ONB** - **4**)³: Under an N₂ atmosphere at room temperature with external cooling, we added powder **3** (213 mg, 1 mmol) to a stirred solution of PBr₃ (0.1 ml, 1.1 mmol) in DCM (10 mL). Stirring was continued at room temperature for 1 h. The reaction mixture was neutralized with a 2 N aqueous NaHCO₃ solution (100 mL). The organic phase was then separated, and the aqueous phase was rinsed twice with DCM (50 mL). The solution was then dried over Na₂SO₄ and the solvent was removed to yield **4** (95%) as slightly yellow needles. ¹H NMR (400 MHz, CDC1₃) δ 7.67 (s, 1 H), 6.93 (s, 1 H), 4.86 (s, 2 H), 3.99 (s, 3 H), 3.96 (s, 3 H). ¹³C NMR (50 MHz, CDCl₃) δ 153.5, 149.2, 140.5, 127.6, 113.9, 108.8, 56.7, 30.2.

3-methyl-2-oxo-2H-chromen-7-yl propionate (5)⁴: A mixture of 2,4-dihydroxybenzaldehyde 3.00 g, sodium propionate 4.50 g, propionic anhydride 7.54 g and piperidine 0.4 ml was stirred under reflux for 6 h. The reaction solution was poured into ice water, the precipitate was collected by filtration and dissolved in EtOAc, the organic layer was washed with water and 1 N HCl. Then it was concentrated and dried over anhydrous Na₂SO₄. The resulting residue was subjected to column chromatography and white crystals of compound 5 in 50 % δ yield were obtained. ^{1}H NMR (400 MHz, $CDCl_3$) 7.50 (s, 1H), 7.40 (d, 1H, J = 8 Hz), 7.08 (d, 1H, J = 2 Hz), 7.00 (dd, 1H, J = 8, 2 Hz), 2.64-2.59 (2H), 2.20 (s, 3H), 1.29-1.25 (3H). ¹³C NMR (100 MHz, CDCl₃) δ 172.5, 162.0, 153.8, 152.3, 138.9, 127.7, 125.2, 118.4, 117.4, 110.1, 27.8, 17.2, 9.1

7-hydroxy-2-oxo-2H-chromene-3-carbaldehyde (**6**)⁵: To a solution of compound **5** (2.7 g, 11.9 mmol) in 75 mL of CCl₄ was added NBS (5.31 g, 29 mmol) and a trace amount of AIBN, and the mixture was then refluxed. After reaction for 8 h, the solvent was removed under reduced pressure. To the resulting residue were added NaOAc (8.78 g, 107 mmol) and acetic acid (80 mL), and the mixture was then heated to reflux for 12 h. Subsequently, 2 N HCl (60 mL) was added to the hot reaction mixture, and the reaction was allowed to continue for 30 min and left to stir at room temperature overnight. The reaction mixture was then evaporated to dryness, and the residue was directly purified by column chromatography to afford **5** in 50 % yield as a yellow powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.86 (s, 1H), 8.20 (s, 1H), 7.89 (d, 1H, *J* = 8.2 Hz), 7.23 (dd, 1H, *J* = 8.2, 2 Hz), 7.21 (d, 1H, *J* = 2 Hz). ¹³C NMR (50 MHz, DMSO-*d*₆) δ 188.2, 165.3, 160.1, 158.0, 147.7, 133.8, 117.6, 114.9, 111.3, 102.7

7-hydroxy-3-(hydroxymethyl)-2*H*-chromen-2-one (**COU** - **7**)⁶: To a stirred solution of **6** (1 g, 5.2 mmol) in methanol (30 mL) was added NaBH₄ (95 mg, 2.5 mmol). The reaction mixture was stirred at RT for 2 hours. After completion of the reaction (by TLC), the reaction mixture was decomposed with ammonium chloride solution and then diluted with EtOAc, washed twice with brine, dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel to give **7** in 80 % yield as a very light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.41 (s, 1H), 7.82 (s, 1H), 7.53 (d, 1H, *J* = 8.2 Hz), 6.76 (dd, 1H, *J* = 8.2, 2.4 Hz), 6.70 (d, 1H, *J* = 2.4 Hz), 4.29 (s, 2H). ¹³C NMR (50 MHz, DMSO-*d*₆) δ 160.9, 160.6, 154.7, 138.4, 129.7, 124.8, 113.5, 111.9, 102.3, 58.6

7-((4,5-dimethoxy-2-nitrobenzyl)oxy)-3-(hydroxymethyl)-2H-chromen-2-one (**8**): Treatment of **7** (82 mg, 0.30mmol) with **4** (57 mg, 0.30 mmol) in the presence of K₂CO₃ (47 mg, 0.34 mmol) in dry DMF at room temperature for a period of 12 h afforded the conjugate as a yellow solid. The crude conjugate was purified by column chromatography to give the compound **8** (65 %) as a light Yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.90 (s, 1H), 7.72-7.69 (2H), 7.33 (s, 1H), 7.12 (s, 1H), 7.04 (d, 1H, *J* = 8.2 Hz), 5.5 (s, 2H), 4.31 (s, 2H), 3.86 (s, 6H). ¹³C NMR (50 MHz, DMSO-*d*₆) δ 160.3, 159.9, 154.0, 153.1, 148.0, 139.9,

137.4, 129.2, 126.3, 125.8, 113.1, 112.7, 111.7, 108.4, 101.5, 67.1, 58.1, 56.2, 56.1. HRMS (ESI+) calcd for C₁₉H₁₇NO₈ [M+Na]⁺, 410.0847; found: 410.0852

3-(bromomethyl)-7-((4,5-dimethoxy-2-nitrobenzyl)oxy)-2H-chromen-2-one (**9**): Under an N₂ atmosphere at room temperature with external cooling, we added powder **8** (387 mg, 1 mmol) to a stirred solution of PBr₃ (0.1 ml, 1.1 mmol) in DMF (5 mL). Stirring was continued at room temperature for 4 h. The reaction mixture was neutralized with a 2 N aqueous NaHCO₃ solution (100 mL) and diluted with EtOAc. The organic phase was then separated, and the organic phase was rinsed twice with brine (2×50 mL). Further, the solution was dried over Na₂SO₄ and solvent was removed to yield **9** (95%) as light yellow color powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.23 (s, 1H), 7.73 (s, 1H), 7.67 (d, 1H, *J* = 8.2 Hz), 7.32 (s, 1H), 7.16 (s, 1H), 7.07 (d, 1H, *J* = 8.2 Hz), 5.52 (s, 2H), 4.52 (s, 2H), 3.87 (s, 6H). ¹³C NMR (50 MHz, DMSO-*d*₆) δ 161.3, 159.3, 154.9, 153.0, 147.9, 142.9, 139.8, 129.9, 125.9, 121.5, 113.1, 112.6, 111.6, 108.3, 101.6, 67.2, 56.1, 56.0, 29.6. HRMS (ESI+) calcd for C₁₉H₁₆BrNO₇ [M+H]⁺, 450.018; found: 450.019

(*Z*)-1-((7-((4,5-dimethoxy-2-nitrobenzyl)oxy)-2-oxo-2*H*-chromen-3-yl)methoxy)-3,3diethyltriaz-1-ene 2-oxide (**ONB-COU-DEA-NONOate - 10**): To a solution of EtN(N₂O₂)Na (75 mg, 0.48 mmol) in 1 ml of dry DMF at 0 C was added **9** (180 mg, 0.4 mmol). The reaction was stirred at room temperature under an argon atmosphere. After 24 h, 20 ml of toluene was added, and the mixture was washed with water (3 x 20 ml). The organic phase was dried with Na₂SO₄, filtered, and evaporated to give the crude product as a yellow oil, which was purified by chromatography on silica gel to give 72 mg (36 % yield) of **10** as a light yellow color powder. ¹H NMR (400 MHz, CDCl₃) δ 7.80 (s, 1H), 7.72 (s, 1H), 7.42 (d, 1H, *J* = 8 Hz), 7.24 (s, 1H), 6.98-6.94 (2H), 5.57 (s, 2H), 5.22 (s, 2H), 3.99-3.96 (6H), 3.16 (q, 4H, *J* = 8 Hz), 1.10 (t, 6H, *J* = 8 Hz). ¹³C NMR (50 MHz, CDCl₃) δ 161.3, 161.0, 155.4, 154.2, 148.6, 140.4, 139.5, 129.2, 127.9, 127.7, 113.4, 113.0, 112.8, 108.5, 102.6, 75.9, 67.8, 56.7, 48.8, 11.7. HRMS (ESI+) calcd for C₂₃H₂₆N₄O₉ [M+Na]⁺, 525.159; found: 525.160



Figure S1: ¹H NMR, ¹³C NMR spectra of 8



Figure S2: ¹H NMR, ¹³C NMR spectra of 9

80

190 180 170 160 150 140 130 120 110 100 90

50

40

30 20

10

mqq 0



Figure S3: ¹H NMR, ¹³C NMR spectra of **10**



Figure S4: HRMS spectrum of 8



Figure S5: HRMS spectrum of 9



Figure S6: HRMS spectrum of 10

Measurement of fluorescence quantum yields

The fluorescence quantum yield (QY) of 7-hydroxy-(coumarin-3-yl)methyl alcohol (COU) was determined by reference point method. Quinine sulfate in 0.1 M H₂SO₄ (literature quantum yield: 0.54) was used as a standard sample to calculate the QY of COU, which was dissolved in acetonitrile/water (3:7). The absorbance values of the solutions the excitation wavelength measured with at were UV–Vis spectrophotometer. Photoluminescence (PL) emission spectra of all the sample solutions were recorded by Hitachi F-7000 fluorescence spectrophotometer at an excitation wavelength of 360 nm.

$$\frac{\phi_{\rm S}}{\phi_{\rm R}} = \frac{Int_{\rm S}}{Int_{\rm R}} \frac{1 - 10^{-A_{\rm R}}}{1 - 10^{-A_{\rm S}}} \frac{\eta_{\rm S}^2}{\eta_{\rm R}^2}$$

Where ϕ represents quantum yield, A represents absorbance at excitation wavelength, Int represents area under the fluorescence curve, and η is refractive index of the medium. The subscripts S and R denote the corresponding parameters

for the sample and reference, respectively. Further the fluorescent quantum yield of COU was calculated to be 0.392.

Photolysis of cascade photocage ONB-COU-DEA-NONOate using UV irradiation (≥ 365 nm) and diode laser (730 nm)

a) Photolysis of ONB-COU-DEA-NONOate using UV irradiation (\geq 365 nm): 5 mL of 1.0×10^{-4} M ACN:H₂O solution (3:7 mixture) of ONB-COU-DEA-NONOate in quartz cuvette, was exposed to UV light source (\geq 365 nm) i.e. 125 W medium pressure Hg vapor lamp using a suitable filter 1 M CuSO4 solution in 0.1 N H₂SO₄. During the course of photolysis, 20 µL of the aliquots were taken at regular intervals of time, and analyzed by RP-HPLC using mobile phase MeOH:H₂O (5:5), at a flow rate of 1 mL/min (detection: UV 254 nm). Peak areas were determined by RP-HPLC (calculated as an average of three runs), which indicated a gradual decrease in the concentration of cascade cage of DEA-NONOate with time. The reaction was followed till the ONB-COU-DEA-NONOate peak area is less than 5 % of the initial area (30 min).

b) Photolysis of ONB-COU-DEA-NONOate using Red laser: 5 mL of 1.0×10^{-4} M ACN:H₂O solution (3:7 mixture) of ONB-COU-DEA-NONOate was taken in quartz cuvette and was irradiated using 730 nm laser diode (30 mW/ cm²). At regular interval of time, 20 µL of the aliquots was taken and analyzed by RP-HPLC using mobile phase MeOH:H₂O (5:5), at a flow rate of 1 mL/min (detection: UV 254 nm).

Detection and estimation of nitric oxide photoreleased during 1 and 2 photon excitation of ONB-COU-DEA-NONOate by Griess assay⁷

The photorelease of nitric oxide has been detected and estimated by performing Griess assay. Griess reagent was freshly prepared by mixing equal volumes of 1% sulphanilamide in 5% orthophosphoric acid and 0.1% naphthylethylenediamine dihydrochloride (NED) in distilled water. 1×10^{-4} M solution of ONB-COU-DEA-NONOate has been treated with Griess reagent and photolysed with both UV light (\geq 365 nm) and 730 nm laser. The absorbance of the photolysed sample has been recorded at regular intervals. Estimation of NO or nitrite (NO_2^{-}) ion was accomplished by recording the increase in the absorbance at ~545 nm corresponding to the formation of azo dye and determining the nitrite concentration of the

sample from the corresponding nitrite calibration curve. The NO released from cascade photocage after photolysis using \geq 365 nm and 730 nm diode laser was quantified to be 110 μ M and 32 μ M respectively.



Figure S7: (a) Absorption recorded at regular intervals during photolysis of ONB-COU-DEA-NONOate (10^{-4} M) (treated with 1 mL of Griess reagent) with UV light (\geq 365 nm) (b) Nitrite concentration standard curve

Enhancement in fluorescence during photolysis of ONB-COU-DEA-NONOate using 1 PE



Figure S8: Emission spectra recorded (λ_{ex} : 325 nm) during photolysis of ONB-COU-DEA-NONOate (10⁻⁴ M in 3:7; ACN:PBS) with UV light for 30 min.

Schematic representation of mechanism for generation of NO from cascade photocage i.e. ONB-COU-DEA-NONOate



Scheme 2: Mechanism for step wise release of cascade photocage i.e. ONB-COU-DEA-NONOate upon 1PE and 2PE

Cytotoxicity studies of ONB-COU-DEA-NONOate on MDA-MB-231 cell line upon 1 PE

i. Before photolysis. The *in vitro* cytotoxicity of ONB-COU-DEA-NONOate and ONB-COU-Ac were measured using the MTT (3–(4,5–dimethylthiazol–2–yl)–2,5–diphenyltetrazolium bromide, a yellow tetrazole) assay on MDA-MB-231 cell line. Briefly, cells growing in log phase were seeded into 96–well cell–culture plate at 5×10³ cells/well. Different concentration of ONB-COU-DEA-NONOate and ONB-COU-Ac (0- 20 μ M) were added in the wells with an equal volume of PBS in the control wells. The cells were then incubated for 24 h at 37 °C in 5% CO₂. Thereafter, fresh media containing 50 μ L MTT (1 mg/mL) was added to the 95 well plates and incubated for 4 h at 37 °C in 5% CO₂. Formazan crystals thus formed were dissolved in DMSO after decanting the earlier media and absorbance recorded at 595 nm.

ii. After photolysis. Cytotoxicity studies have been carried out in two sets. a) Dosedependent cytotoxicity study b) Time dependent cytotoxicity study

(a) Dose-dependent cytotoxicity study. MDA-MB-231 cells maintained in minimum essential medium (in 96-well cell-culture plate at concentration of 1×10^4 cells/mL) containing 10 % fetal bovine serum (FBS) and different concentrations (0-20 μ M) of ONB-COU-DEA-NONOate and ONB-COU-Ac were incubated for 4 h at 37 °C and 5 % CO₂. Then the

cells were irradiated using UV light (30 min). After irradiation the cells were again incubated for 24 h. Then cytotoxicity was measured using the MTT assay as described earlier.

(b) Time dependent cytotoxicity study. Similarly time dependent cytotoxicity study has been carried out by fixing the concentration of ONB-COU-DEA-NONOate to be incubated as 10 μ M and measuring the cytotoxicity by MTT assay at different durations of time exposure of cells (i.e. at 0 min, 10 min, 20 min, 30 min) to UV light.



Figure S9: (a) Time dependent photoinduced cytotoxicity obtained upon exposing ONB-COU-DEA-NONOate treated MDB-MA-231 cells to UV light (\geq 365 nm) for different time intervals. Values are presented as means ± standard deviations of three different observations.

Time dependent cell imaging study of ONB-COU-DEA-NONOate on MDA-MB-231 cell line

To visualize the photorelease of nitric oxide *in vitro* time dependent cell imaging study of ONB-COU-DEA-NONOate has been performed. Briefly, MDA-MB-231 cell (1.5×10^4) were seeded on each coverslips placed in 60 mm petri plate and allowed to adhere and attain the spreaded morphology. Cells were then incubated with 10 µM of ONB-COU-DEA-NONOate in cell culture medium for 4 h at 37 °C and 5 % CO2. Then the cells were irradiated (keeping the cell-culture plate 5 cm apart from the light source) using 125 W medium pressure Hg lamp as irradiation source (\geq 365 nm) and 1M CuSO₄ solution as cut-off filter for 30 min. Thereafter, cells were fixed in 3.7 % paraformaldehyde for 15 min, washed two times with PBS, and was followed by permanent mounting with DPX for confocal microscopic imaging

(CLSM, Olympus FluoView FV1000). The sample was then focused and observed on confocal microscope with imaging software, FV10- ASW2.0 Viewer.



Figure S10. Fluorescence emitted from ONB-COU-DEA-NONOate treated cells after exposure to different indicated UV irradiation times

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