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Youhei Chitose, Manabu Abe, Ko Furukawa, Jhe-Yi Lin, Tzu-Chau Lin, et al.. Design and Synthesis of a Caged Carboxylic Acid with a Donor- $\pi$ -Donor Coumarin Structure: One-photon and Two-photon Uncaging Reactions Using Visible and Near-Infrared Lights. *Organic Letters*, 2017, 19 (10), pp.2622-2625. 10.1021/acs.orglett.7b00957 . hal-01527343

**HAL Id: hal-01527343**

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Submitted on 30 May 2017

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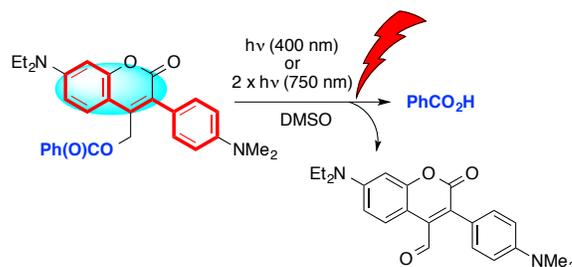
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# Design and Synthesis of a Caged Carboxylic Acid with a Donor- $\pi$ -Donor Coumarin Structure: One-photon and Two-photon Uncaging Reactions Using Visible and Near-Infrared Lights

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**ABSTRACT:** A caged carboxylic acid with a novel TP-responsive D(donor)- $\pi$ -D coumarin backbone with a quadrupolar nature was designed and synthesized in this study. The newly synthesized coumarin derivative showed a strong one-photon (OP) absorption band ( $\epsilon \sim 29000 \text{ cm}^{-1} \text{ M}^{-1}$ ) in the visible region ( $> \sim 400 \text{ nm}$ ). Time-dependent density functional theory calculations predicted a sizable TP absorption cross-section with a maximum at  $\sim 650 \text{ nm}$  significantly larger than that related to the OP absorption band. This is confirmed experimentally using TP excited fluorescence in the fs regime that leads to TPA cross-section of 18 GM and 5.6 GM at 680 nm and 760 nm, respectively. The OP photolysis (400 nm) and NIR-TP photolysis (750 nm) of the caged benzoic acid resulted in a clean formation of benzoic acid and an aldehyde.

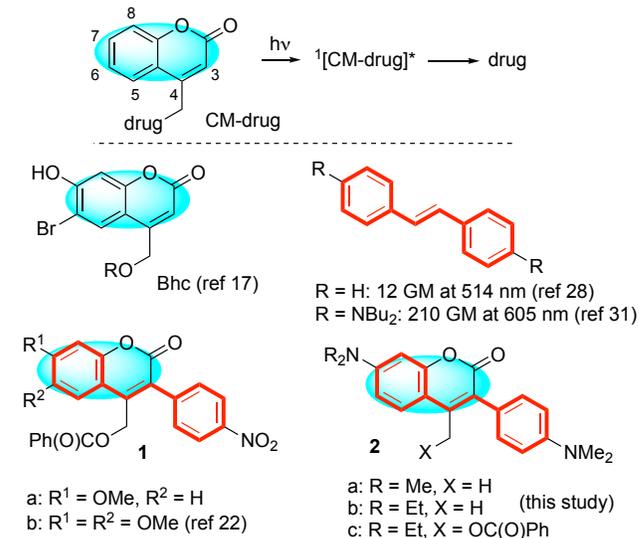


Caged compounds, which are temporally inactivated forms of bioactive substances by photolabile-protecting groups (PPGs), are widely used in various studies to understand the behaviors of bioactive compounds.<sup>1–4</sup> The phototriggered release of bioactive molecules (drugs) without using any chemical reagents plays an important role in physiological studies.

Coumarin-based caged compounds (CM-drug) were developed by Givens and Matuszewski (Figure 1).<sup>5</sup> The fast release of bioactive compounds (drug) from the singlet excited state,  $^1[\text{CM-drug}]^*$ , is an advantage that allows their use in physiological studies.<sup>6,7</sup> However, coumarins exhibit absorption wavelength in the region 280–300 nm.<sup>8,9</sup> UV irradiation is needed to generate the excited state using one-photon (OP) excitation, causing cell damage. The unfavorable damage can be avoided by red-shifting the absorption maximum to the visible-light region. This has been achieved by the introduction of electron-donating and/or withdrawing substituents at the C5–C8 positions.<sup>10–12</sup>

Two-photon (TP) excitation processes using light in the near-infrared (NIR) region, 650–1050 nm, are advantageous for physiological studies, because deep penetration and a high spatial resolution can be achieved.<sup>13–16</sup> The development of new NIR-TP-responsive chromophores is currently a state-of-the-art challenge. Several  $\pi$ -extended coumarin derivatives

with TP absorption (TPA) character have been synthesized.<sup>17–22</sup> Furuta *et al.* developed a TP-responsive (6-bromo-7-



**Figure 1.** Photochemical uncaging reaction. Coumarin-based Chromophores with TPA character.

hydroxycoumarin-4yl)methyl (Bhc) group (Figure 1),<sup>17</sup> which has a TP uncaging efficiency ( $\delta_u$ ) of  $\sim 1 \text{ GM}$  at 740 nm ( $\delta_u = \sigma_2$

$\times \phi_u$ , where  $\sigma_2$  is the TPA cross-section (GM)<sup>23</sup> and  $\phi_u$  is the uncaging quantum yield). A higher TP efficiency would be better for physiological studies.<sup>24</sup>

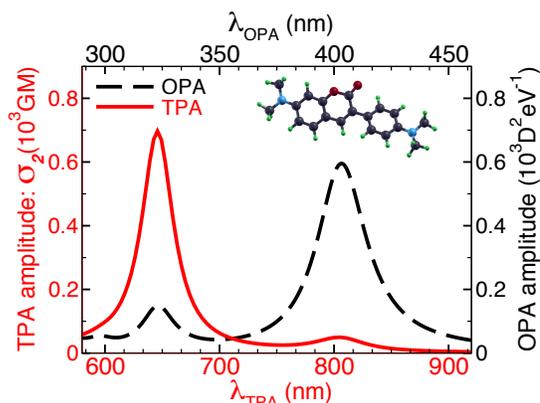
So far, we have designed and synthesized TP chromophores with a stilbene core as the platform,<sup>25–27</sup> because stilbene itself has a relatively large TPA cross-section, 12 GM at 514 nm, despite a small  $\pi$  conjugation system.<sup>28</sup> Donor (D)–acceptor (A)  $\pi$ -conjugated<sup>29</sup> coumarin derivatives **1** (Figure 1) showed TP-induced uncaging in the NIR region, in which an electron-withdrawing group was introduced at the C3 position.<sup>22</sup> However, low quantum yields of 0.09 and 0.03 were observed for the uncaging reactions of **1a** and **1b**, respectively, decreasing the efficiency of the TP-induced uncaging reactions.

This paper describes the synthesis and reactivity of a novel D- $\pi$ -D conjugated coumarin-based caged compound **2** (Figure 1), in which the D-substitution at the C3 position was achieved for the first time. The D- $\pi$ -D structural motifs were reported to significantly enhance the TPA character in stilbene cores because of a large change in quadrupole moment during the electronic excitation process.<sup>30,31</sup> For example, 4,4'-bis(di-*n*-butylamino)-*E*-stilbene was reported to exhibit a large TP cross-section of 210 GM at 605 nm (Figure 1). Such a high TP cross-section due to the D- $\pi$ -D structural motif is worthy of application in caged compounds. The D- $\pi$ -D structural motif by introducing the donating substituent at the C3 position has not been applied so far to coumarin-4ylmethyl type of caged compounds.

First, the OP absorption (OPA) and TPA spectra of a coumarin derivative **2a** were predicted using density functional theory (DFT) and time-dependent (TD) DFT approaches (Figure 2). The computational details are provided in Supporting Information. The predicted first absorption maximum of 7-dimethylamino-substituted coumarin ( $S_0 \rightarrow S_1$  transition) is slightly blue-shifted compared to its D- $\pi$ -A analogue **1a** (Figure S19)<sup>22</sup>. As expected for a D- $\pi$ -D chromophores, a large TPA cross-section (of ca. 700 GM at this level of theory, see discussion on the supporting information for more details) was found for **2a** near 650 nm, corresponding to the  $S_0 \rightarrow S_2$  electronic transition. Such a larger TPA cross-section of the second electronic transition ( $S_0 \rightarrow S_2$ ) as compared to that of the first electronic transition ( $S_0 \rightarrow S_1$ ) is similar to the one reported on 4,4'-bis(di-*n*-butylamino)-*E*-stilbene<sup>31</sup>. These computational predictions inspired us to synthesize caged benzoic acid **2c**, in which the OPA should occur in the visible region whereas TP uncaging should be possible using excitation in the NIR region.

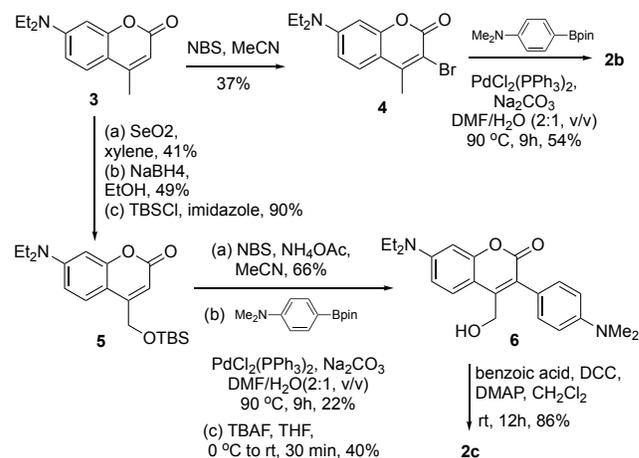
7-(Diethylamino)-3-(4-(dimethylamino)phenyl)-4-methyl-2*H*-chromen-2-one (**2b**) with a D- $\pi$ -D  $\pi$ -conjugated coumarin chromophore was synthesized as shown in Scheme 1. Bromination of commercially available 7-diethylamino-substituted coumarin **3** gave compound **4**;<sup>21</sup> subsequent coupling with the pinacol ester of 4-dimethylaminophenyl boronic acid afforded **2b**. Consistently with the TD-DFT prediction, compound **2b** showed a first OPA band with an absorption maximum at 386 nm ( $\epsilon = 28861 \text{ cm}^{-1} \text{ M}^{-1}$ ) in DMSO (Figure S11).

The TPA spectrum of compound **2b** ( $1.0 \times 10^{-4} \text{ M}$ ) was



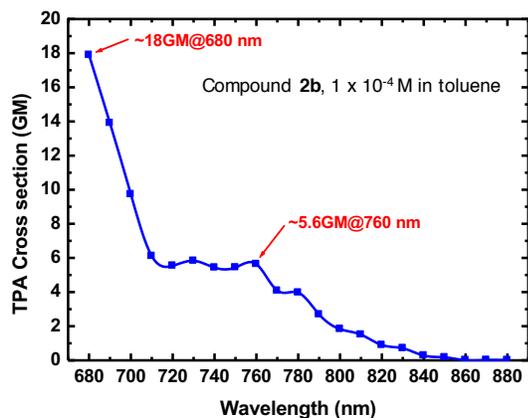
**Figure 2.** Computed OPA (right-hand axis) and TPA (left-hand axis) spectra at the TD-B3LYP/6-31G(d)//B3LYP/6-31G(d) level of theory for a coumarin derivative **2a**, in vacuum and using a damping factor of 0.10 eV to simulate the finite linewidth in the resonant spectra.

### Scheme 1. Synthesis of compound **2b** and **2c**.



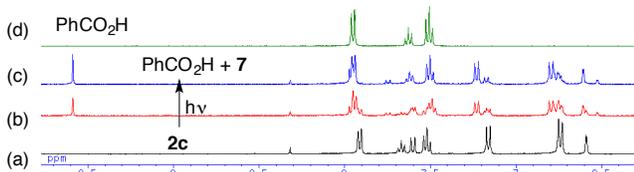
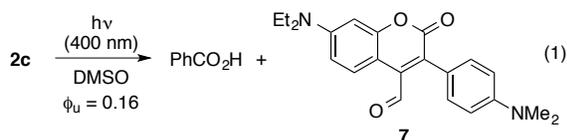
measured using the TP excitation fluorescence method in toluene, even though the dynamic tuning range of our laser system for the measurements is limited over 680-nm excitation wavelength (Figure 3). As predicted by the TD-DFT calculations (Figure 2), the TPA cross-section of the second electronic transition ( $S_0 \rightarrow S_2$ , < 680 nm) was much larger than that of the first electronic transition ( $S_0 \rightarrow S_1$ , ~760 nm), i.e., 5.6 GM at 760 nm and 18 GM at 680 nm.

Compound **2c** was also synthesized from compound **3** (Scheme 1). After the oxidation of **3** with  $\text{SeO}_2$  and protection of the alcohol, the rigid D- $\pi$ -D stilbene structure was prepared by introducing the electron-donating group at the C3 position using the coupling of the bromide with the commercially available pinacol ester of 4-dimethylaminophenyl boronic acid. The corresponding 4-hydroxy methyl derivative **6** was synthesized by deprotection. Caged benzoic acid **2c** was obtained by condensation with benzoic acid in a high yield (86%). The UV–visible absorption spectrum of compound **2c** showed the maximum absorption at 407 nm ( $\epsilon_{407\text{nm}} = 28493 \text{ M}^{-1} \text{ cm}^{-1}$ ) in DMSO (Figure S14).



**Figure 3.** TPA spectrum, 680–880 nm, of compound **2b** ( $1.0 \times 10^{-4}$  M) in toluene.

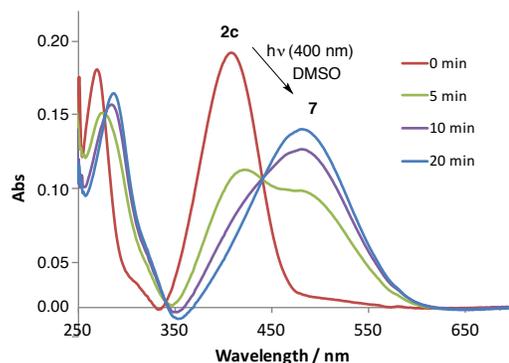
The OP photolysis of compound **2c** was conducted using a Xe lamp at  $400 \pm 10$  nm in DMSO- $d_6$  (1.8 mM), resulting in the quantitative uncaging of benzoic acid (Eq. 1, Figure 4). The quantum yield ( $\phi_u$ ) was determined to be 0.16. After 2-h irradiation, the photoproduct 4-carboxyaldehyde coumarin **7** was isolated in 70% yield along with benzoic acid (~95%). The formation of an aldehyde was observed for the first time in related uncaging reactions using coumarin derivatives. The clean photochemical transformation of **2c** was also confirmed by analysis of UV–visible absorption spectra (Figure 5). Thus, aldehyde **7** with  $\lambda_{\max} = 482$  nm ( $\epsilon$  23178  $\text{cm}^{-1} \text{M}^{-1}$ ) was observed with a concomitant decay of the band of **2c** with  $\lambda_{\max}$  407 nm.



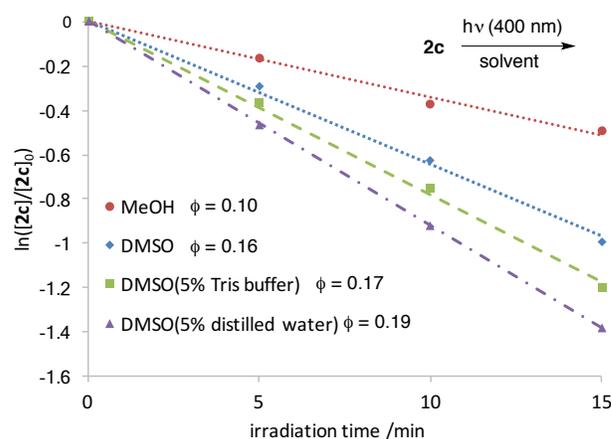
**Figure 4.** OP uncaging reaction of compound **2c** at  $400 \pm 10$  nm in DMSO- $d_6$ ; (a)  $^1\text{H}$ NMR spectrum of compound **2c** in DMSO- $d_6$  before the irradiation; (b) after 1-h photolysis using 400 nm (b); after 2-h photolysis; (c)  $^1\text{H}$ NMR spectrum of benzoic acid in DMSO- $d_6$ .

The effect of solvent on the OP photolysis of compound **2c** was investigated using methanol, DMSO with 5% Tris buffer, and DMSO with 5% distilled water (Figure 6). The uncaging reaction rates of coumarin-4ylmethyl type caged compounds were reported to be fast in the presence of water in solvents.<sup>18</sup> Interestingly, the uncaging reaction of **2c** in methanol was slower than the reaction in anhydrous or wet DMSO (5% tris buffer) by a factor of 1.6 (Figure 6). However, the reaction rate of uncaging of **2c** in wet DMSO (5% water) was slightly faster than anhydrous DMSO by a factor of 1.2 (Figure 6). 4-Hydroxymethyl derivative **6** was isolated in 76% isolated yield in wet DMSO in place of aldehyde **7** in anhydrous DMSO (Scheme 2). The formation of photoproducts clearly suggests that carbocation **8** is generated in the photochemical reaction,

which is trapped by DMSO or  $\text{H}_2\text{O}$ , affording aldehyde **7** or alcohol **6** (Scheme 2).<sup>6</sup> The significantly short lifetime of  $^1\text{2c}^*$  fluorescence (577 ps in DMSO) in comparison with  $^1\text{2b}^*$  (3.1 ns, Figures S12,S13) supports the fast release of benzoic acid from  $^1\text{2c}^*$  (Figures S15, S16).



**Figure 5.** UV–visible spectroscopic analysis of OP uncaging reaction of caged benzoate **2c** at  $400 \pm 10$  nm irradiation in DMSO.

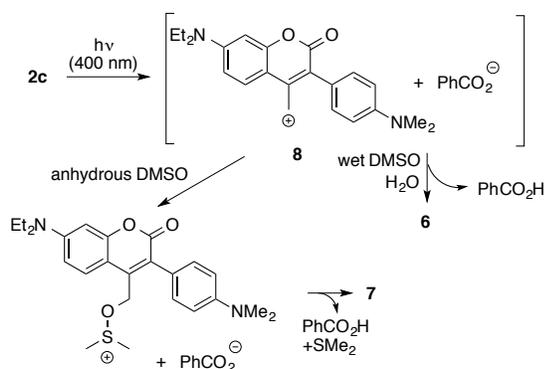


**Figure 6.** Time profile of the OP uncaging of compound **2c**,  $\ln[2c]/[2c]_0$  vs. irradiation time (min) at a wavelength of 400 nm using a Xe lamp in various solvents.

Finally, the TP photolysis of compound **2c** ( $5 \times 10^{-2}$  mM) was carried out in DMSO using 750-nm light obtained from a Ti:sapphire laser (pulse width 100 fs, 80 MHz) at an average power of 700 mW (Figure S17). The TP-uncaging reaction of **2c** was observed at 750 nm, and the uncaging rate was determined to be  $k_{750} = 1.9 \times 10^{-6} \text{ s}^{-1}$ . The TPA cross-section of **2c** was extrapolated to  $\sim 7$  GM at 750 nm by comparing the uncaging rate constant of  $9.4 \times 10^{-6} \text{ s}^{-1}$  of the standard compound NPBF-BA ( $\sigma_2 = 54$  GM and  $\phi_u = 0.09$ )<sup>26</sup>. This TPA cross-section is consistent with the TPA spectrum recorded for **2b** (Figure 3). Although we cannot experimentally measure the TPA cross-section value of **2b** below 680 nm, due to the limitation of our laser setup, the cross-section at the maximum can be extrapolated from the computationally predicted cross-sections by using simple proportionality method as described in the SI. Therefore, the maximal TPA cross-section of compound **2c** can be estimated to reach  $\sim 100$  GM around 650 nm. The corresponding TP uncaging efficiency was then estimated to be  $\sim 16$  GM ( $= 100 \times 0.16$ ), which is one order of magnitude larger than that of related dipolar coumarin derivatives.

In this study, a novel caged carboxylic acid with a TP-responsive D- $\pi$ -D coumarin backbone was designed and synthesized. The newly synthesized D- $\pi$ -D-substituted coumarin derivative showed a strong OPA band ( $\epsilon \sim 29000 \text{ cm}^{-1} \text{ M}^{-1}$ ) in the visible region ( $> \sim 400 \text{ nm}$ ). TD-DFT calculations predicted that the TP excitation process of the second electronic transition is allowed, with a maximum of several hundreds of GM at  $\sim 650 \text{ nm}$ . Meanwhile, the TPA cross-section of the first electronic transition close to  $800 \text{ nm}$  was predicted to be much smaller, as a result of the quadrupolar nature of the investigated compound. In fact, the experimental TPA cross-section at  $680 \text{ nm}$  was found three times larger (18 GM) than that recorded in the vicinity of twice the wavelength of the main OPA band (5.6 GM at  $760 \text{ nm}$ ). The OP photolysis of **2c** with a D- $\pi$ -D coumarin backbone in DMSO resulted in a clean formation of benzoic acid and an aldehyde **7**, hitherto unknown in coumarin-4-yl methyl type uncaging reactions. The quantum yield of 0.16 was much higher than the D- $\pi$ -A-substituted coumarin derivative. In the presence of  $\text{H}_2\text{O}$ , alcohol **6** was formed in place of the aldehyde, suggesting the generation of coumarin 4-ylmethyl cation **8** in the uncaging reaction. This new platform for the TP-induced uncaging reaction can be applied to future *in vivo* physiological studies.

**Scheme 2.** Mechanism for the uncaging reaction of **2c** in anhydrous DMSO and wet DMSO.



### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Computational and experimental details,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for new compounds (PDF)

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#### ACKNOWLEDGMENT

NMR and MS measurements were performed at N-BARD, Hiroshima University. M.A. gratefully acknowledges the financial support by a Grant-in-Aid for Science Research on Innovative Areas “Stimuli-responsive Chemical Species (No. 2408)” (JSPS KAKENHI Grant No. JP24109008) and JP17H0302200. TCL acknowledges the financial support from the Ministry of Science and Technology (MOST), Taiwan (Grant No. MOST 105-2113-M-008-004). C.K. acknowledges the HPC resources of CINES and IDRIS under the allocations 2016-[x2016080649] made by GENCI.

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