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A new caging phototrigger based on a 2-acetonaphthyl chromophore

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Abstract—Irradiation ($\lambda \sim 350$ nm in an aqueous environment) of carboxylic acid esters derived from the reaction between carboxylic acids and 2-bromo-1-(naphthalene-2-yl)ethanone affords the parent carboxylic acid in good yield, making the 2-acetonaphthyl chromophore a good phototrigger for caging applications, including biomolecular caging.

Molecular caging is a technique in which a bioactive compound is rendered inactive by covalently linking it to a photolabile group. The caged molecule can be released in its active form by photoirradiation of the cage.[1–4] The caging technique is used in many areas such as analytical chemistry, biochemistry, combinatorial chemistry, materials chemistry, medicine, organic synthesis, and physiology, and it offers numerous practical applications. For instance, while biomolecular arrays based on photocleavable cages are of central importance in the field of nanotechnology, the possibility of prodrug photoactivation and site-, time- and concentration-controlled photorelease of drugs is important in the field of medicine and healthcare. Further, it presents a novel strategy for in vivo investigation of a wide range of cellular activities.

Many phototriggers have been developed for caging applications. While phototriggers that are photoactivable in organic media employing UV light can be used in synthesis, combinatorial chemistry, analytical chemistry, and in many other non-biological situations, such phototriggers are of limited use in biological and medical applications. In this context, we have recently synthesized and examined the efficacy of phototriggers based on nitronaphthyl and anthryl frameworks.[5–7]

For biological and medical caging applications, the phototrigger should have a high rate and quantum yield of photoreaction, a biologically benign photoproduct and the photoactivation of the chromophore should occur under physiological conditions. Recently, novel phototriggers based on a phenacyl chromophore have attracted much attention.[8–15] The phenacyl chromophore has found varied caging applications, for example, in caging of phosphates,[8] excitatory amino acids[9] and peptides,[10] and photoreversible covalent inhibition of protein tyrosine phosphatases.[11] Noteworthy attempts have been made to develop improved phototriggers based on an acetophenone chromophore.[8,16] Herein, we report a new phototrigger based on a 2-acetonaphthyl chromophore, which can find applications in caging of bioactive compounds through a carboxylic functional group (Scheme 1).

In order to investigate the phototrigger properties of the 2-acetonaphthyl chromophore, we first prepared 2-bromo-1-(naphthylen-2-yl)ethanone (**2**) by brominating 2-acetonaphthalene following a previously described procedure.[13,17] Subsequently, esters **5a**–**5e** were obtained in good yields by treating various carboxylic acids with **2** in the presence of triethylamine in dry acetonitrile at ambient temperature for 12 h. Additionally, 2-bromo-1-(4-methoxyphenyl)ethanone (**4**), a known phototrigger was prepared for comparison purposes from 4-methoxyacetophenone (**3**) as described elsewhere.[17] All compounds were characterized by IR, ^{1}H NMR and mass spectroscopy.[18]

A solution of **2** in THF–H_2O (1:1, v/v) showed absorption up to 380 nm (ε, 220 M L^{-1} cm^{-1}) with an absorption maximum (λ_{max}) at 346 nm (ε, 2992 M L^{-1} cm^{-1}). However, **4** in the same solvent showed λ_{max} at 284 nm (ε, 17433 M L^{-1} cm^{-1}) with no significant

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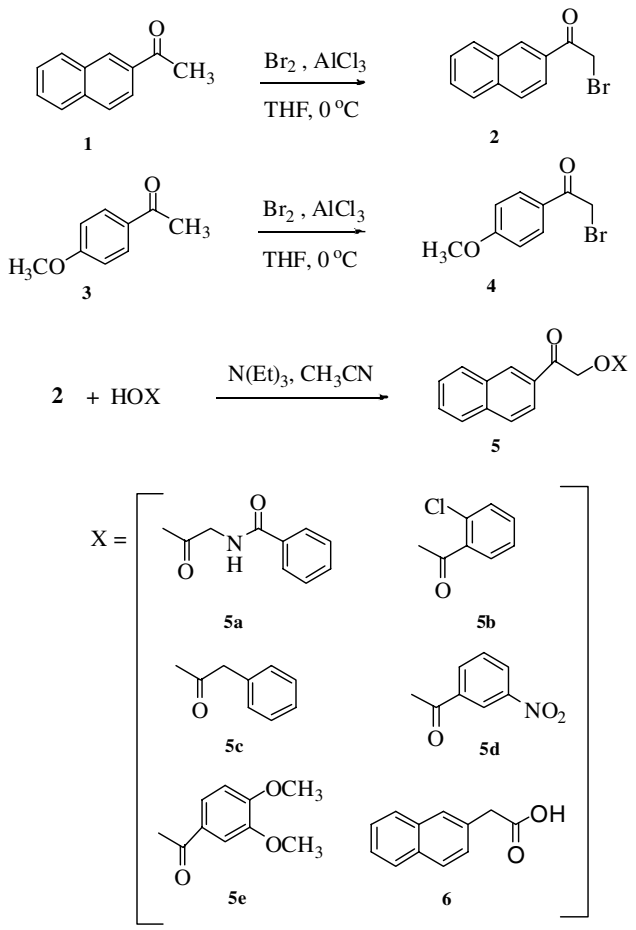


Scheme 1.

absorption beyond 350 nm (ε, 192 M L^{-1} cm^{-1}). The photocleavable protecting group properties of the esters derived from **4** are known, and besides release of the protected moiety, reduced and rearrangement photoproducts are known to form.[8,16,19] Photo-debromination of **2** is known and after debromination it subsequently undergoes a neophenyl-like rearrangement.[20] The photolysis of **2** in THF–H_2O (1:1, v/v, 1.0×10^{-3} M) at $\geqslant$337 nm yielded three products, two of which were characterized by HPLC and ^{1}H NMR analysis as the reduced 2-acetonaphthone (**1**) and the rearrangement photoproduct naphthalene-2-acetic acid[21] (**6**). HPLC analysis of the photomixture of **2** obtained after photolysis at $\geqslant$337 in 1,4-dioxane–H_2O (1:1, v/v) and in CH_3CN–H_2O (1:1, v/v) showed a similar profile of photoproducts. Thus, the photochemistry of **2** did not change significantly with solvent systems.

The UV–vis absorption spectra of esters **5a**–**5e** were similar to that of the parent chromophore (2-acetonaphthyl) present in **2**. Photolysis of **5a** in THF–H_2O (1:1, v/v) released the parent acid and **1** along with a few other minor photoproducts, which could not be characterized. Similar results were observed when esters (**5b**–**5e**) were photolyzed. Typical absorption spectral changes during the photolysis of ester **5a** is shown in Figure 1 and the photochemical data for esters **5a**–**5e** are summarized in Table 1. Maximum photorelease yields of 88% and 90% were observed for **5a** and **5e** when photolyzed at $\geqslant$337 nm in THF–H_2O (1:1, v/v) mixture, with the time taken for complete consumption of the starting material being 2–4 h. Good photorelease yields were also obtained in the case of ester **5c**. However, in the cases of esters **5b** and **5d**, the photorelease yield was moderate. The quantum yield (Φ) for the starting esters varied in the range 0.068 to 0.180 at 350 nm.[22] When a solution of **5a** in THF–H_2O (1:1)

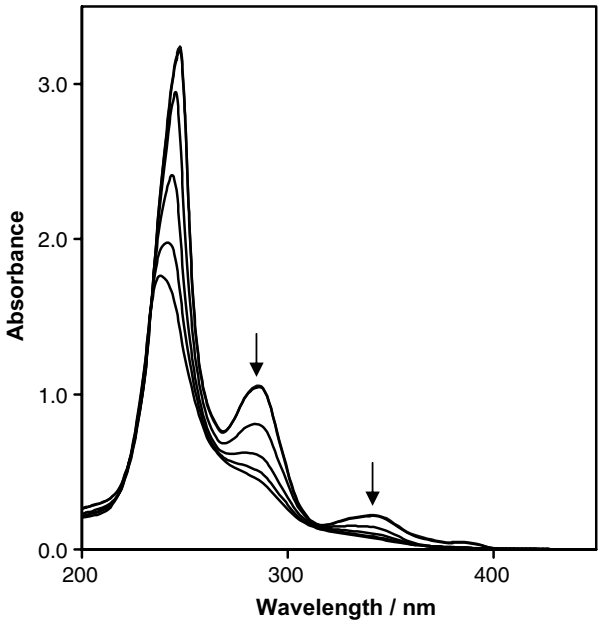
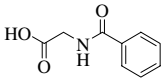
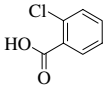
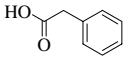
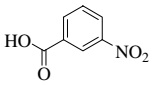
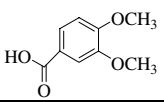
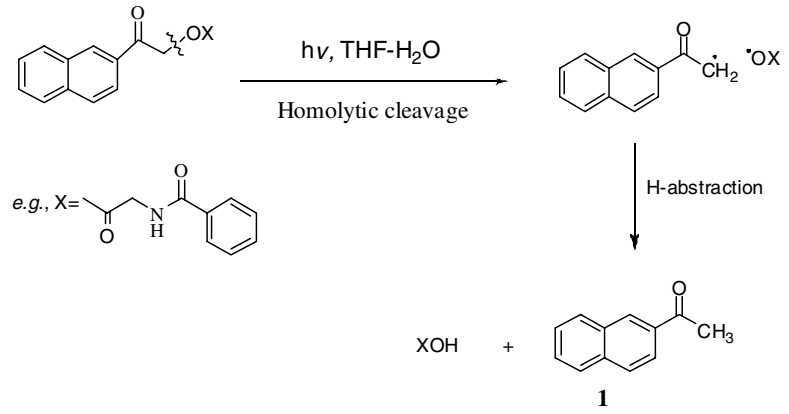


Figure 1. UV–vis absorption spectral changes during photolysis of ester **5a** at 350 nm in THF–H_2O (1:1, v/v, 1.0×10^{-4} M).

Table 1. Photochemical properties of esters **5a**–**5e** in THF–H_2O (1:1, v/v)

Ester	Carboxylic acid	Photorelease yield[a] (%)	Photolysis[b] time (h)	Φ_{PR}[c]
5a		88	2.3	0.117
5b		42	5	0.068
5c		67	3	0.180
5d		44	5	0.080
5e		90	4	0.120

[a] Based on HPLC.
[b] Time for complete disappearance of starting ester (1.0×10^{-3} M).
[c] Quantum yield of disappearance of the starting ester at 350 nm at ambient temperature.



Scheme 2.

was photolyzed at longer wavelength ($\geqslant$370 nm), similar photoproducts were obtained, with a maximum photorelease yield of 94%. Parallel dark reactions were conducted for all the esters and it was found that no thermal reaction occurred under the photolysis conditions. To find the best solvent system for the photolysis, **5a** was photolyzed in different solvent systems including THF–H_2O (7:3, v/v), THF–H_2O (3:7, v/v), CH_3CN–H_2O (1:1, v/v) and 1,4-dioxane–H_2O (1:1, v/v). The best photorelease yield of 88% was obtained in THF–H_2O (1:1, v/v).

During the photolysis of esters **5a**–**5 e**, the release of carboxylic acid was accompanied by the appearance of the reduced photoproduct **1**. Based on a literature precedence, a plausible mechanism for the observed photochemistry of the esters is outlined in Scheme 2.[8,16,19] Thus, homolytic cleavage of the C–O bond leads to the formation of a radical pair, which, among many other possible reactions, on subsequent hydrogen atom abstraction gives **1** and the carboxylic acid.

In conclusion, esters bearing a 2-acetonaphthyl chromophore can be photoexcited in aqueous medium at 350 nm, releasing the corresponding carboxylic acids in good chemical yields. This work introduces a new potential phototrigger, which is useful for various caging applications.

Acknowledgements

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18. A typical procedure for the preparation of esters **5a**–**5e**: A solution of **2** (0.8 mmol) and carboxylic acid (0.9 mmol) in dry CH_3CN (10 mL) was cooled to 0 °C. The cooled solution was treated with triethylamine (0.9 mmol) dropwise over 15 min and then stirred at ambient temperature. The progress of the reaction was monitored by TLC (silica gel). After completion, the reaction mixture was neutralized with aq. HCl and then poured into water, extracted with ethyl acetate and dried. Removal of the solvent under reduced pressure yielded a solid, which was further purified by column chromatography. Compound **5a**: Yield: 60%; mp: 79–81 °C; FTIR (KBr) ν_{max} (cm^{-1}): 3392 (NH), 1720 (CO), 1666 (OCO) and 1633 (NHCO); ES-MS: *m/z* Found 348.1219 (M^++H) calculated for $C_{21}H_{18}NO_4$ 348.1236 (M^++H); ^1H NMR (300 MHz, $CDCl_3$): δ 8.42 (s, 1H, Ar-H), 7.99–7.82 (m, 6H, Ar-H), 7.67–7.42 (m, 5H, Ar-H), 6.79 (br s, 1H, NH), 5.60 (s, 2H, CH_2O) and 4.51 (d, $J = 5.1$ Hz, 2H, CH_2). Compound **5b**: Yield: 69%; mp: 79–81 °C; FTIR (KBr) ν_{max} (cm^{-1}): 1743 (OCO) and 1710 (CO); ES-MS: *m/z* Found 347.0453 (M^++Na) calculated for $C_{19}H_{13}O_3ClNa$ 347.0451 (M^++Na); ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H, Ar-H), 8.10–7.90 (m, 5H, Ar-H), 7.67–7.36 (m, 5H, Ar-H) and 5.74 (s, 2H, CH_2). Compound **5c**: Yield: 57%; mp:

96–98 °C; FTIR (KBr) v_{max} (cm^{-1}): 1743 (OCO) and 1696 (CO); ES-MS: *m/z* Found 327.1013 (M^++Na) calculated for $C_{20}H_{16}O_3Na$ 327.0997 (M^++Na); ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H, Ar-H), 7.97–7.87 (m, 5H, Ar-H), 7.64–7.57 (m, 3H, Ar-H), 7.39–7.27 (m, 3H, Ar-H), 5.49 (s, 2H, CH_2) and 3.85 (s, 2H, CH_2). Compound **5d**: Yield: 65%; mp: 136–138 °C; FTIR (KBr) v_{max} (cm^{-1}): 1743 (OCO), 1710 (CO), 1532 and 1354 (NO_2); GC–MS, *m/z* (% rel int): 335 (M^+, 0.5), 305 (9), 155 (100), 127 (47) and 92 (20); ^1H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H, Ar-H), 8.49 (m, 3H, Ar-H), 8.01–7.91 (m, 4H, Ar-H), 7.73–7.60 (m, 3H, Ar-H) and 5.80 (s, 2H, CH_2). Compound **5e**: Yield: 60%; mp: 110–112 °C; FTIR (KBr) v_{max} (cm^{-1}): 1737 (OCO) and 1690 (CO); ES-MS: *m/z* Found 373.1035 (M^++Na) calculated for $C_{21}H_{18}O_5Na$ 373.1052 (M^++Na); ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H, Ar-H), 8.05–7.88 (m, 4H, Ar-H), 7.64–7.55 (m, 2H, Ar-H), 7.32–7.28 (m, 1H, Ar-H), 6.56 (d, 2H, $J = 8.4$ Hz, Ar-H), 5.65 (s, 2H, CH_2) and 3.80 (s, 6H, $2 \times OCH_3$).

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