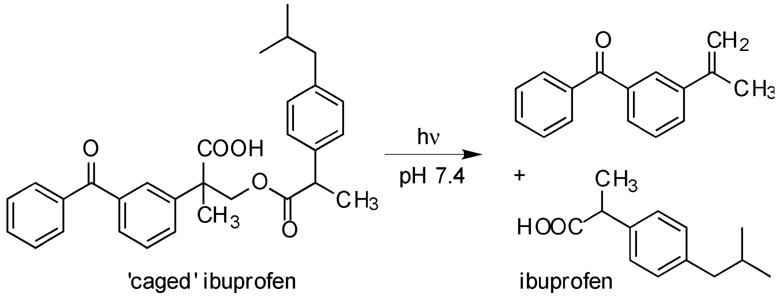
Communication

Carbanion-Mediated Photocages: Rapid and Efficient Photorelease with Aqueous Compatibility

Matthew Lukeman, and Juan C. Scaiano

J. Am. Chem. Soc., **2005**, 127 (21), 7698-7699• DOI: 10.1021/ja0517062 • Publication Date (Web): 06 May 2005



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
COMMUNICATIONS

Carbanion-Mediated Photocages: Rapid and Efficient Photorelease with Aqueous Compatibility

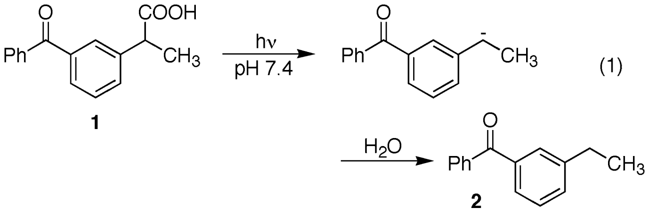
Matthew Lukeman and Juan C. Scaiano*

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario K1N 6N5, Canada

Received March 17, 2005; E-mail: tito@photo.chem.uottawa.ca

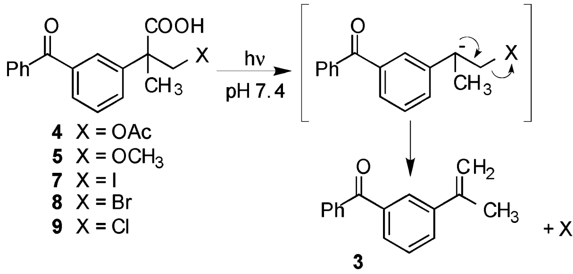
Photoremovable protecting groups or “photocages” provide biochemists with powerful tools for the rapid introduction of a variety of compounds to biological systems with spatial and temporal control, allowing the time-resolved study of the ensuing events.[1] They have found use in other fields ranging from molecular array (biochip) synthesis to time-resolved X-ray crystallography. The most widely used photocage, the *o*-nitrobenzyl (*o*NB) group, suffers from major disadvantages, specifically, slow release rate following excitation (typically several microseconds or longer), poor aqueous solubility, and formation of reactive nitrosoaldehyde byproducts.[2] Much effort has been devoted to the development of new photocages that overcome one or more of the drawbacks associated with the *o*NB group, although no candidate has emerged with a sufficiently desirable combination of properties to challenge its dominance. We report the development of a new photocage that is superior to the *o*NB group in several respects, including a release rate improvement of over 1000-fold, a higher photorelease quantum yield, excellent aqueous solubility, and formation of benign photoproducts. This photocage is capable of releasing a wide variety of biologically relevant substrates, including alcohols and carboxylic acids.

The design of the new photocage has its roots in the photochemistry of ketoprofen (**1**), a nonsteroidal anti-inflammatory drug (NSAID). On electronic excitation in neutral aqueous media, **1** undergoes rapid and efficient decarboxylation ($\Phi = 0.75$) to give a benzylic carbanion, which is rapidly protonated by the solvent ($k \sim 4.9 \times 10^6$ s^{-1}) to give 3-ethylbenzophenone (**2**) (eq 1).[3] We sought to harness this efficient photochemistry for effecting photorelease by creating derivatives that include an appropriate leaving group substituted β to the photogenerated carbanion. Elimination would release the leaving group in its active form, along with 3-(2′-allyl)benzophenone (**3**) (eq 2). This reaction represents a novel carbanion-mediated mechanism for photodecaging and is mechanistically unrelated to other photodecaging reactions that involve a benzophenone moiety.[4]

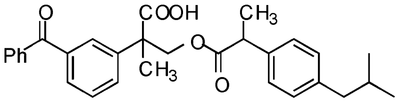


(1)

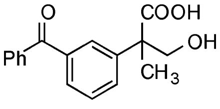
Derivatives **4** and **5** were synthesized to test the viability of this design toward photorelease of carboxylic acids and alcohols, respectively, while derivative **6** was designed to photorelease ibuprofen to demonstrate possible drug release applications. In addition, derivatives **7**−**9** bearing iodide, bromide, and chloride leaving groups, respectively, were also prepared and studied. Esters **4** and **6** were synthesized by treatment of the corresponding alcohol **10** with the anhydride or acid chloride of acetic acid and ibuprofen, respectively. Alcohol **10** was obtained via addition of gaseous formaldehyde to the anion of the *tert*-butyl ester of **1**, followed by deprotection with TiCl$_4$. Methyl ether **5** was obtained by treatment of the anion of the methyl ester of **1** with iodomethyl methyl ether, followed by hydrolysis in dilute NaOH solution. Derivatives **7**−**9** were prepared by addition of diiodomethane, dibromomethane, or iodochloromethane, respectively, to the anion of 2-benzoylphenylpropionitrile, followed by hydrolysis to the corresponding acid in 50% H$_2$SO$_4$.



(2)

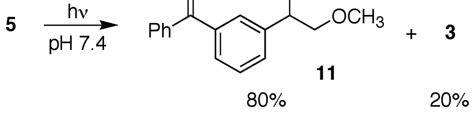


6



10

Dilute deoxygenated solutions (4 mM) in phosphate buffer (pH 7.4) were prepared and irradiated briefly (1−10 min) with UVA light (λ 350 nm) and, following workup, were analyzed by ^{1}H and ^{13}C NMR and MS. The only photoproduct observed on irradiation under these conditions for derivatives **4** and **6**−**9** was **3**, indicating that the photogenerated carbanion gives quantitative photorelease of all carboxylic acids and halides examined, with protonation of the intermediate carbanion by water not being competitive. The efficiency of the photorelease was very high for these derivatives ($\Phi \sim 0.7$) and is more than sufficient for biochemical applications. Derivative **5** bearing a strongly basic leaving group (methoxide) gave **3** in 20% yield, along with an 80% yield of **11**, the product corresponding to protonation of the intermediate carbanion (eq 3). While elimination of simple alcohols from the decarboxylated ketoprofenate cage is not quantitative, the quantum yield is still in the range of 0.10−0.15, which is adequate for most applications.



(3)

An important concern in application of “ketoprofenate” photocages is the possible formation of radicals or other reactive species resulting from secondary photolysis of the photoproduct **3** that might

10.1021/ja0517062 CCC: $30.25

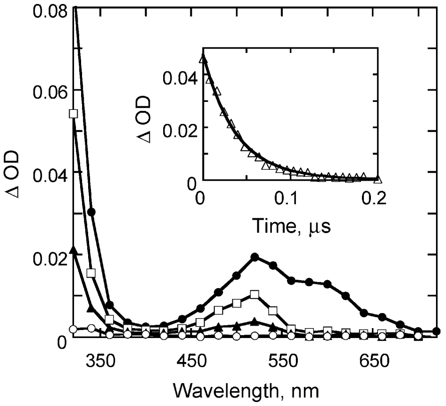


Figure 1. Transient absorption spectrum observed for **4** in phosphate buffer solution (pH 7.4) at 72 (▲), 180 (○), 460 (▲), and 1650 (○) ns after the laser pulse ($\tau = 308$ nm). Inset: decay profile for absorption at 600 nm with first-order kinetic fit.

interfere with the system under study. To test for possible secondary photochemistry, a pure sample of **3** was chromatographically separated from the photolyzate of a solution of **4** and was irradiated alongside an equimolar sample of **4** in aqueous acetonitrile solution (1:1, aqueous portion buffered at pH 7.4). Under irradiation conditions that gave 80% decaging of acetate from **4**, absolutely no decomposition of **3** was observed (by GC−MS), indicating that **3** can be considered photoinert under the conditions relevant to photorelease applications; this probably reflects lower excited-state energies (compared to that of benzophenone) and the π,π^* character of its low-lying excited states.

The protonation rate constants (in water) of a series of benzoyl benzyl carbanions have been measured by laser flash photolysis (LFP) and vary between 2×10^6 and 2×10^7 s^{-1}, depending on the nature of the benzylic substituents.[5] Assuming that ≥99% of the carbanions generated from **4** and **6**−**9** undergo elimination, a minimum photorelease rate constant of $\geq 2 \times 10^8$ s^{-1} can be estimated, which is more than 2 orders of magnitude faster than that for release of carboxylic acids from the *o*NB chromophore.[2a] The fast rate constant for carboxylate elimination precludes the detection of the proposed intermediate carbanion by conventional nanosecond LFP. Elimination of methoxide from **5**, however, is slower, as protonation of the intermediate carbanion is competitive, thus nanosecond LFP was employed in an attempt to detect the carbanion intermediate. LFP of a flowing solution of **5** (oxygen-saturated phosphate buffer, pH 7.4, λ_{ex} 308 nm) gave rise to two kinetically distinct transient species, both present immediately after the laser pulse (Figure 1). The longer-lived species at λ_{max} 520 nm is characteristic of the triplet excited state of the benzophenone chromophore[3b] and is assigned as such. The shorter-lived species with λ_{max} 580 nm and $\tau = 40$ ns is assigned to the expected carbanion intermediate based on the similarity of its maximum absorption and lifetime with that of previously reported ketoprofen-derived carbanions.[3] From the partitioning between the elimination and protonation routes, we calculate a rate constant for methoxide elimination from **5** of 5.1×10^6 s^{-1}. This rate constant is more than 6 orders of magnitude higher than that for photorelease of alcohols from *o*NB ethers and for alcohols linked to other photocages through carbonate or carbamate linkers![2,6] Ketoprofenate-protected alcohols might, therefore, be the most attractive entry into the study of submillisecond biological processes. Methoxide photorelease can be viewed as the limiting case; any better leaving group should eliminate with a faster rate constant and higher quantum yield, suggesting that the ketoprofenate cage could be successfully applied to the photorelease of other biologically significant functional groups, including phosphates.

In addition to the high quantum yields and fast photorelease rates, the ketoprofenate cage offers other advantages over the *o*NB group. The carboxylate function imparts excellent aqueous solubility to the caged group. Also, photorelease can only proceed from the carboxylate form (that is present at neutral pH), so no special handling precautions are required to avoid exposure of the caged group to light prior to loading in the aqueous medium.

In their recent review on photocages,[1a] Pelliciolli and Wirz outlined what they believed to be the six most important criteria that the ideal photocage would meet (in the context of biological applications), and they include the following: (1) clean and efficient photochemistry; (2) adequate absorption at wavelengths longer than 300 nm; (3) good aqueous solubility; (4) generation of inert and nonabsorbing photoproducts; (5) high decaging rate constant; and (6) absence of "dark" activity (from release via thermal hydrolysis, for example). The ketoprofenate chromophore satisfies all six criteria outlined by Pelliciolli and Wirz and, thus, is a significant step forward in the evolution of photocaging chromophores.[7] In summary, we report the successful design of a new photocaging group capable of effecting rapid and efficient photorelease of carboxylic acids, halides, and alcohols, and potentially many other functional groups, that possesses several advantages over the conventional *o*NB group.

Acknowledgment. We acknowledge the generous financial support of the Natural Sciences and Engineering Research Council of Canada (NSERC). M.L. thanks NSERC for a postdoctoral fellowship.

Supporting Information Available: Experimental preparations for **4**−**9** and ^{1}H NMR spectra for **4** and **5** before and after irradiation (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Pelliciolli, A. P.; Wirz, J. *Photochem. Photobiol. Sci.* **2002**, *1*, 441. (b) Givens, R. S.; Conrad, P. G., II; Yousef, A. L.; Lee, J.-I. In *CRC Handbook of Photochemistry*, 2nd ed.; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; Chapter 69.
(2) (a) Il'ichev, Y. V.; Schwörer, M. A.; Wirz, J. *J. Am. Chem. Soc.* **2004**, *126*, 4581. (b) Corrie, J. E. T.; Barth, A.; Munasinghe, V. R. N.; Trentham, D. R.; Hutter, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 8546−8554.
(3) (a) Boscá, F.; Marin, F. L.; Miranda, M. A. *Photochem. Photobiol.* **2001**, *74*, 637−655. (b) Cosa, G.; Martinez, L. J.; Scaiano, J. C. *Phys. Chem. Chem. Phys.* **1999**, *1*, 3533−3537. (c) Martinez, L. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 11066−11070. (d) Monti, S.; Sortino, S.; De Guidi, G.; Marconi, G. *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 2269−2275.
(4) (a) Cossy, J.; Rakotoarisoa, H. *Tetrahedron Lett.* **2000**, *41*, 2097−2099. (b) Papageorgiou, G.; Ogden, G.; Corrie, J. E. T. *J. Org. Chem.* **2004**, *69*, 7228−7233. (c) Papageorgiou, G.; Lukeman, M.; Wan, P.; Corrie, J. E. T. *Photochem. Photobiol. Sci.* **2004**, *3*, 366−373.
(5) (a) Cosa, G.; Llauger, L.; Scaiano, J. C.; Miranda, M. A. *Org. Lett.* **2002**, *4*, 3083. (b) Llauger, L.; Cosa, G.; Scaiano, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 15308−15312.
(6) Papageorgiou, G.; Barth, A.; Corrie, J. E. T. *Photochem. Photobiol. Sci.* **2005**, *4*, 216−220.
(7) Photoproduct **3** has an absorption profile that is very similar to that of the starting acids **4**−**9** at wavelengths longer than 300 nm, and while **3** is not "nonabsorbing" (criterion 4), no highly absorbing photoproducts are formed, unlike the photoproducts arising from the *o*NB group.

JA0517062