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Wavelength-selective cleavage of photolabile protecting groups

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Abstract

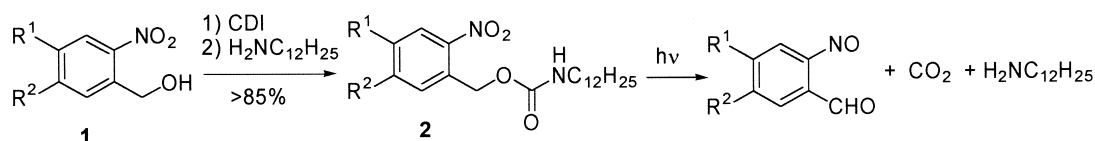
The selective photocleavage of protecting groups using monochromatic light is described. Some groups were found to react faster than others at 254 nm, whereas this trend was reversed at 419 nm. This behavior was preserved in solution mixtures of both groups. The selective control of which group is activated is thus achieved by using an influence external to the reaction mixture. © 2000 Elsevier Science Ltd. All rights reserved.

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Photochemical reactions are very appealing processes from both economical and environmental aspects. Indeed, light is a very cheap reagent, and it does not generate chemical waste.¹ These features have, however, been hampered for decades by a lack of selectivity and sometimes quite unpredictable results. One area in organic photochemistry showing an ever-increasing activity is the photodeprotection of functional groups.² The absence of chemical reagents indeed makes this process very tolerant towards otherwise sensitive functionalities. Very ingenious applications have been developed, such as biologically active ‘caged’ molecules³ (which are liberated at their relevant site by irradiation with UV-light) or spatially addressable combinatorial libraries.⁴ Despite the useful technologies that have been developed so far, it would be highly desirable to have the same kind of selectivity that is found for conventional chemical reactions. One of the only handles available to tune the properties of the light is its wavelength. We recently initiated a program aimed at developing selective photochemical reactions promoted by monochromatic light of specific wavelength, and we disclose here our preliminary results in the area of photodeprotection of functional groups.

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The most widely used photolabile protecting groups are based on Patchornik and Woodward's 2-nitroveratrole-derived carbamates⁵ (NVOC), such as **2a** (Scheme 1). Their photolysis liberates the free amine, carbon dioxide and an *o*-nitrosobenzaldehyde derivative. As it is well established, the substitution pattern around the aromatic ring dramatically alters the absorbance in the UV–vis spectra.⁶ Since the rate of reaction of the photodeprotection process is proportional to its ability to capture a photon at a specific wavelength,⁷ we hypothesized that a series of analogues of **2a** with variable substitutions would have different photolysis rates according to the irradiation wavelength.



Scheme 1.

To this end, the carbamates **2a–f** were prepared by the coupling of 1-dodecylamine and the corresponding benzylic alcohols **1a–f** with 1,1'-carbonyldiimidazole,⁸ in yields consistently higher than 85%. The alcohol **1c** was prepared by benzylic bromination of the 4-bromo-2-nitrotoluene, followed by displacement with potassium acetate and saponification,⁹ whereas the other alcohols were commercially available. The carbamate **2g** was prepared by simple aromatic nucleophilic substitution of the chloride **2e** with piperidine (98%), and **2h** by a fluoride-mediated Suzuki coupling with the bromide **2c**^{10,11} (76%). The carbamates **2a–h** were photolyzed in acetonitrile and the deprotection rate and half-lives were determined by ¹H NMR at different wavelengths.¹² These results are summarized in Table 1.

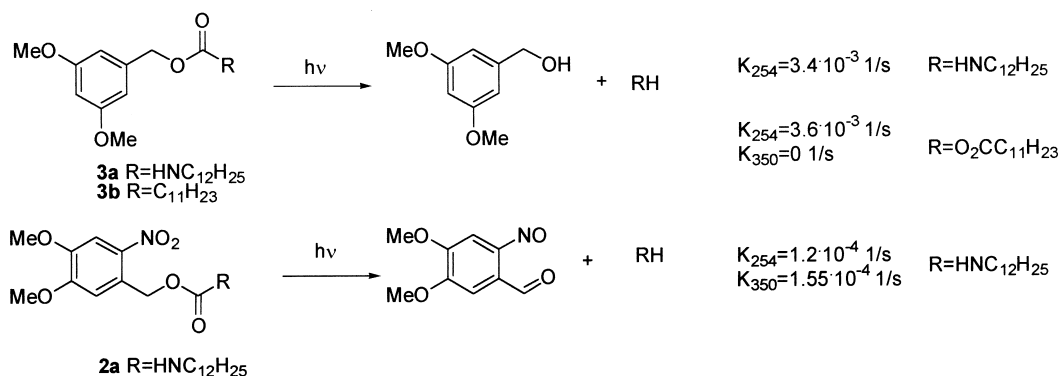
Table 1
Rate of photolysis of the carbamates **2a–h** in MeCN at 30°C

Entry	carbamate	R ¹	R ²	k _{254nm}	k _{420nm}	t _{1/2(254)}	t _{1/2(420)}
1	2a	OMe	OMe	118·10 ⁻⁶	35·10 ⁻⁶	98 min	330 min
2	2b	NO ₂	H	209·10 ⁻⁶	25·10 ⁻⁶	55 min	462 min
3	2c	Br	H	403·10 ⁻⁶	20·10 ⁻⁶	29 min	578 min
4	2d	Cl	H	432·10 ⁻⁶	24·10 ⁻⁶	27 min	481 min
5	2e	H	Cl	240·10 ⁻⁶	21·10 ⁻⁶	48 min	550 min
6	2f	H	H	243·10 ⁻⁶	27·10 ⁻⁶	47 min	420 min
7	2g	H	1-piperidyl	38·10 ⁻⁶	~ 0	304 min	stable
8	2h	Ph	H	830·10 ⁻⁶	30·10 ⁻⁶	14 min	385 min

It is immediately apparent from Table 1 that some candidates have to be discarded as potential photolabile groups. For example, an electron-donating group *para* to the strongly electron-withdrawing nitro group (entry 7) greatly enhanced the absorbance at longer wavelengths ($\epsilon = 17880$, $\lambda = 396$ nm), but drastically reduced the reaction rates. On the other hand, the bromo

derivative **2c** and the NVOC-derivative **2a** showed complementary behavior: **2c** reacted faster than **2a** at 254 nm by a factor of 3.4, whereas at 419 nm, this trend was reversed by a factor of 1.8. Our original hypothesis was thus validated, but the quite modest rate differences prompted us to consider other families of photolabile groups.

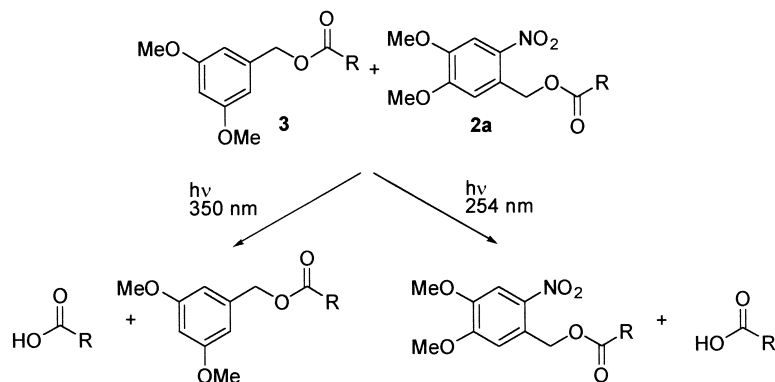
The 3,5-dimethoxybenzyl alcohol derivatives are also known to be cleaved by light,¹³ and the absence of a nitro group was expected to reduce the absorbance at longer wavelength. Indeed, the deprotection rate of **3b** was close to zero at 350 nm, but was exceedingly fast at 254 nm for both carbamates and esters (Scheme 2).



Scheme 2.

This behavior was complementary with the carbamate **2a**, with a rate constant ratio higher than 30:1 at 254 nm, and lower than 1:100 at 350 nm, opening the prospect for a selective liberation of either an acid or a base by only the choice of the wavelength.

Encouraged by these results, we then attempted the *simultaneous* and *selective* deprotection of a mixture of ester **3b** and carbamate **2a**, first under a 254 nm irradiation (Scheme 3).



Scheme 3.

To our disappointment, the trend found for individual compounds was not followed as mixtures. The highly reactive (at 254 nm) compound **3b** seemed to act as a sensitizer for the other, less reactive, species **2a**¹⁴ (Fig. 1). This phenomenon was however not general. A similar experiment with an equimolar mixture of **2a** and **2c** showed no variation of the photolysis rate from the pure solutions (Fig. 2). Clearly, intermolecular energy transfer did not operate in this system. In other words, *it was possible to individually address each of the two photolabile groups in the presence of the other by the choice of the irradiation wavelength.*

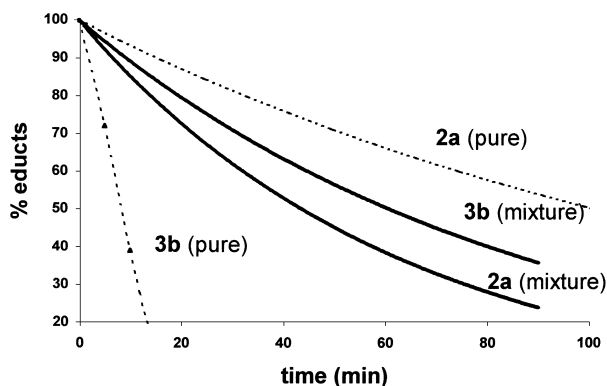


Figure 1. Photolysis of a **3b/2a** mixture at 254 nm

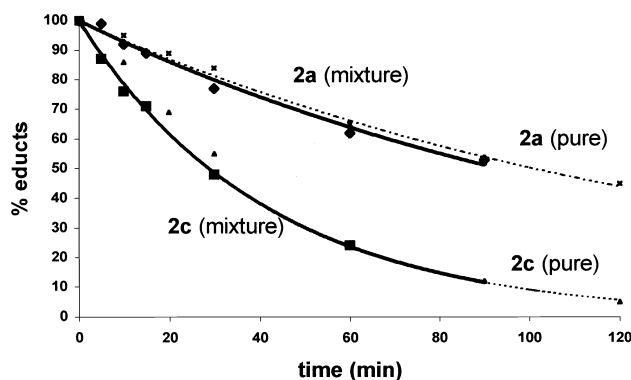


Figure 2. Photolysis of a **2a/2c** mixture at 254 nm

Fig. 3 shows the ¹H NMR portion of the benzylic hydrogens of a near equimolar **2a/2c** mixture in CDCl₃, after increasing irradiation time. We can see that it is indeed possible to selectively deprotect the high-energy labile group from **2c** at 254 nm *in the presence of the low-energy labile group 2a*, and, to a smaller extent, vice versa at a low energy 419 nm light.¹⁵ However, fast cleavage at a short-wavelength UV-light (254 nm) is essential, in order to avoid undesired reactions of conventional protecting groups (such as benzyloxycarbonyl) or peptide degradation. Non-interference of these groups has been shown by Chamberlin using Vycor glass (essentially transparent at 254 nm) filtered light.¹³

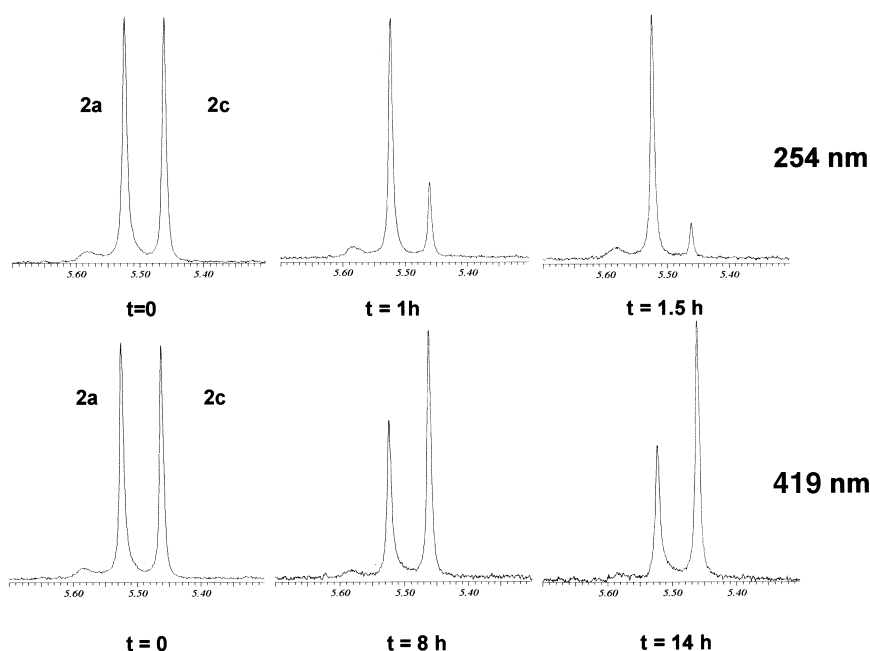


Figure 3. ^1H NMR of the benzylic protons of an equimolar mixture of **2a/2c** after increasing irradiation time. The vertical scale is adjusted to reflect the relative concentrations

In conclusion, we were able to show that differential reactivity of photolabile protecting groups with monochromatic light¹⁶ can be tuned by changing the substitution pattern around the aromatic ring. Although the selectivity factors are still modest, this new concept should open new perspectives in orthogonal protection of functionalities, in automated organic synthesis, and particularly in spatially addressable combinatorial libraries. In the latter application, immobilization of the reacting species on a solid support will play a key role in the intermolecular energy transfer process.¹⁷ This issue is currently being addressed in our laboratory and the results will be reported in due course.

Acknowledgements

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 11. All new compounds showed satisfactory spectroscopic data.
 12. Typical experimental procedure: 25 mg of the carbamate were dissolved in 15 ml of UV-grade acetonitrile in a quartz vessel. The solution was deaerated by a stream of argon for 15 min, and the mixture was irradiated at the desired wavelength in a Rayonet apparatus equipped with 16 fluorescent tubes: RPR2539 (254 nm), RPR3000 (300 nm), RPR 3500 (350 nm) or RPR 4190 (419 nm). Aliquots were taken after a given time, the solvent was evaporated and the residue was analyzed by ¹H NMR in CDCl₃.
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 15. As this work aims at studying the reactivity versus the wavelength, no attempt was made to optimize the formation of amine. It is a known fact that the amine can react with the aldehyde formed, and various solutions have been proposed (see Ref. 5 and 14). After 120 min irradiation, **3a** and **3c** produced, respectively, 19 and 30% of *n*-dodecylamine (characterized as the *N*-tosyl derivative).
 16. By monochromatic light, we designate a light with a wavelength distribution centered around the nominal wavelength. The half-height width is estimated by the manufacturer as 35 nm.
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