

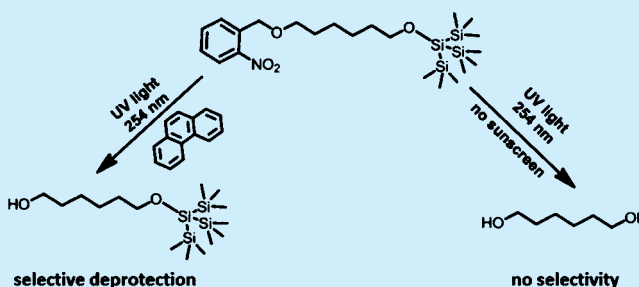
Modulation of Photodeprotection by the Sunscreen Protocol

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Supporting Information

ABSTRACT: A protocol for the selective photoremoval of alcohol protecting groups modulated by the presence of auxiliary light absorbing molecules is presented. Thus, by this method, a single light source was used to selectively remove a specific protecting group in the presence of another chromophore with a lower molar absorption coefficient. The use of a molecular sunscreen, either internal or external, was found to be crucial to achieve high selectivities.



The development of novel methods for selective removal of protecting groups in organic synthesis has been of paramount importance for the achievement of great feats in the construction of complex molecules.¹ Naturally, an ideal synthesis would be rid of protection–deprotection steps;² unfortunately, in most cases this is not possible and in order to acquire the desired scaffolds, chemical protective groups must be added. When more than two protective groups are needed, these must be removed in a selective or even orthogonal manner;³ for example, under the right conditions, the popular *tert*-butyldimethylsilyl (TBS) or *tert*-butyl diphenyl silyl (TBDPS) ether will remain while the trimethylsilyl (TMS) ether group is hydrolyzed completely.⁴ Harsher conditions can then remove TBS or TBDPS when it is no longer needed.

The use of light as a deprotection tool has the advantage that it is usually harmless toward other chemical functionalities found in the molecule. Thus, the development of several photoremovable protecting groups (PPG) and photocages^{5–10} has been well received by expert practitioners of the art of organic synthesis. More recently, Bochet et al. have put forth the chromatic orthogonality concept^{3,11–14} where two different protecting groups may be removed with light of a different wavelength, a concept that was then developed and modified by others.^{15–17} Herein, we present a new method, by which protecting groups with different absorption coefficients may be selectively removed with a single light source in the presence of either an internal or external “sunscreen” accessory.

The photodeprotection of tris(trimethylsilyl)silyl (silyl) protected alcohols by 254 nm UV light is a quite useful and well-studied reaction.¹⁸ Taking into account the low molar absorption coefficients of silyl ethers at shortwave UV, we deemed it a good starting point to look into the photodeprotection of tris(trimethylsilyl)silyloxy octane (**1a**) in the presence of several light absorbing molecules that would act as molecular sunscreens. As shown in Figure 1, phenanthrene was found as the most efficient sunscreen to prevent silyl deprotection, consistent with the fact that phenanthrene has the largest molar absorption coefficient ($\sim 35\,000\text{ M}^{-1}\text{ cm}^{-1}$ at

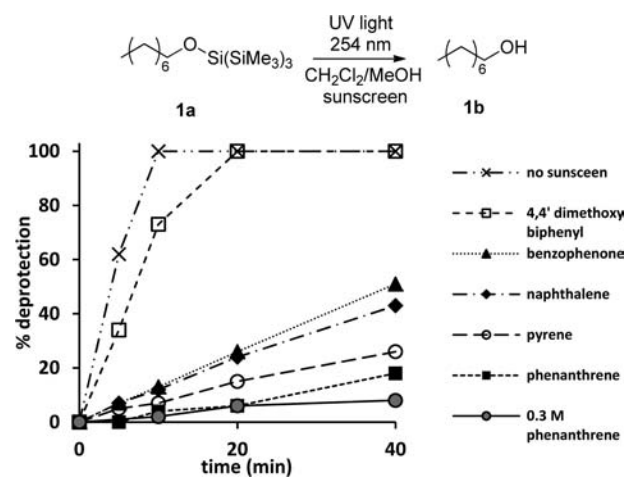


Figure 1. Photodeprotection of tris(trimethylsilyl)silyloxy octane in the presence of light absorbing molecules. Reaction conditions: 0.03 M protected alcohol, 0.1 M sunscreen (unless otherwise indicated), 0.3 M methanol- d_4 (10 equiv), in 1 mL of CD_2Cl_2 irradiated by 254 nm light. Deprotection conversions measured by 1H NMR.

254 nm) compared to the other molecules tested (see Supporting Information).

Having determined this, the efficacy of photocleavage protection by phenanthrene was also examined at different concentrations and also the use of an external solution of phenanthrene surrounding the vial¹⁹ with **1a** (Table 1).

Next, the effect of using the same sunscreen on the photodeprotection of 2-nitrobenzyl-pentanol (**2a**) was examined. The 2-nitrobenzyl group family is a well-known and common PPG for alcohols and other functional groups.^{20–23} 2-Nitrobenzyl protected alcohols have molar absorption coefficients of about 4 times higher at 254 nm than those of

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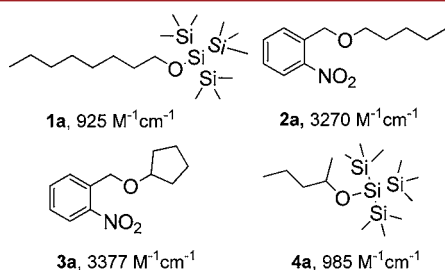
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Table 1. External Sunscreen Effect on Photodeprotection of Tris(trimethylsilyl)Silyloxy Octane in 254 nm UV Light^a

time (min)	external sunscreen (0.1 M phenanthrene)	internal sunscreen (0.1 M phenanthrene)	no sunscreen
	1a:1b		
0	100:0	100:0	100:0
5	100:0	100:0	66:34
15	100:0	95:5	0:100
30	100:0	89:11	0:100
60	100:0	81:19	0:100

^aReaction conditions: 0.03 M protected alcohol, methanol-d₄ (10 equiv), in 1 mL of CD₂Cl₂, irradiated by 254 nm UV light in quartz NMR tube. Deprotection conversion measured by ¹H NMR.

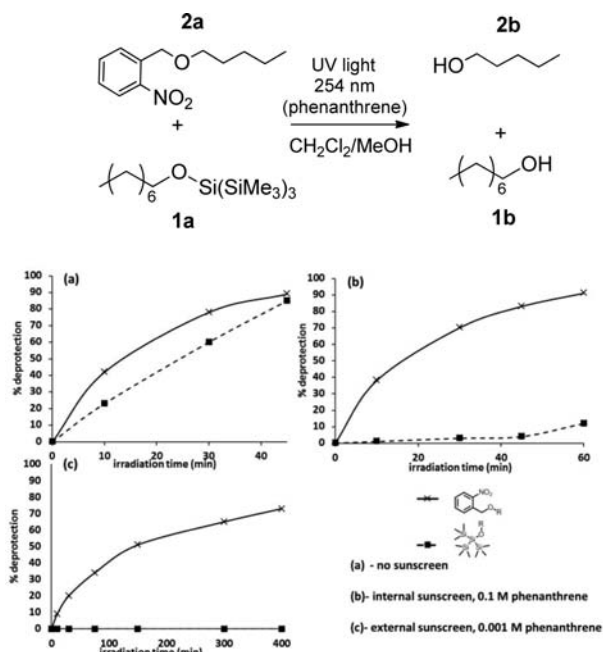
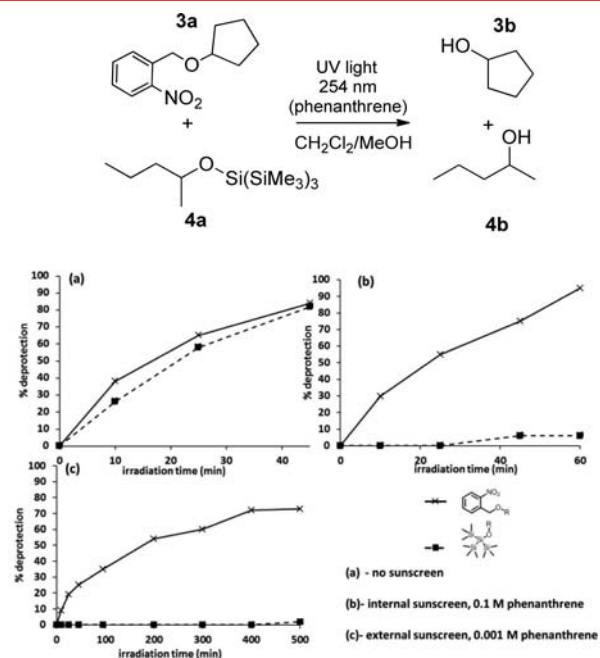
tris(trimethylsilyl)silyl (sisyl) protected alcohols (Figure 2). Indeed, although the deprotection was slowed in the presence of phenanthrene, the reaction still proceeded at an appreciable rate (see Supporting Information).

**Figure 2.** Measured molar absorption coefficients at 254 nm (CH₂Cl₂).

Encouraged by the significant difference in the photocleavage sequences for both PPGs, an experiment was set up with both sisyl and 2-nitrobenzyl ethers present in solution. Thus, pentanol and octanol were protected with 2-nitrobenzyl and sisyl respectively and irradiated with 254 nm light in a CH₂Cl₂ solution in the presence and absence of phenanthrene (both internal and external). The results are illustrated in Figure 3.

The scope of the reaction was probed also for secondary alcohols with very similar results as shown in Figure 4.

Having shown that indeed sisyl and 2-nitrobenzyl protecting groups may be selectively photocleaved by the judicious use of a sunscreen, two diol scaffolds were protected with both protecting groups to afford compounds 5a and 6a. A selective deprotection sequence in these molecules would mimic challenges that may arise within complex organic molecules.^{24,25} Once again, as shown in Figures 5 and 6, even within the same molecular scaffold, the use of the sunscreen method afforded the selective photocleavage of the more sensitive protecting group. Notably, compound 6a is a bisphenol molecule, expanding the sunscreen deprotection method to this type of alcohols as well. The selective deprotection of 5a to afford 5b was carried out in a preparative scale using the internal protection protocol and afforded 82% isolated yields, providing an attractive alternative methodology for selective cleavage of protecting groups with light from a single source. As a control experiment the photocleavage reactions were conducted with lower power light sources to determine whether selectivity could be achieved by this fashion. Even though the 2-nitrobenzyl ether was cleaved at a higher rate, the selectivity produced by the sunscreen protocol could

**Figure 3.** Selective photodeprotection of *o*-nitro [(pentyl)oxy]methyl] benzene and tris(trimethylsilyl) silyloxy octane. Reaction conditions: 0.03 M of protected alcohol, methanol-d₄ (5 equiv), and specified concentration of sunscreen in 1 mL of CD₂Cl₂ irradiated by 254 nm UV light. Deprotection conversion measured by ¹H NMR. Internal standard: 1 equiv of 1,3,5 trioxane.**Figure 4.** Selective photodeprotection of *o*-nitro [(cyclopentyl)oxy]methyl] benzene and 2-tris(trimethylsilyl)silyloxy pentane in the presence of phenanthrene. Reaction conditions: 0.03 M of protected alcohol, methanol-d₄ (5 equiv), and specified concentration of sunscreen in 1 mL of CD₂Cl₂, irradiated by 254 nm UV light. Deprotection conversions measured by ¹H NMR.

not be reproduced (see Supporting Information). In addition, while the intensity of the light is very difficult to tune, it is quite simple to change the concentration of the sunscreen to achieve optimal results.

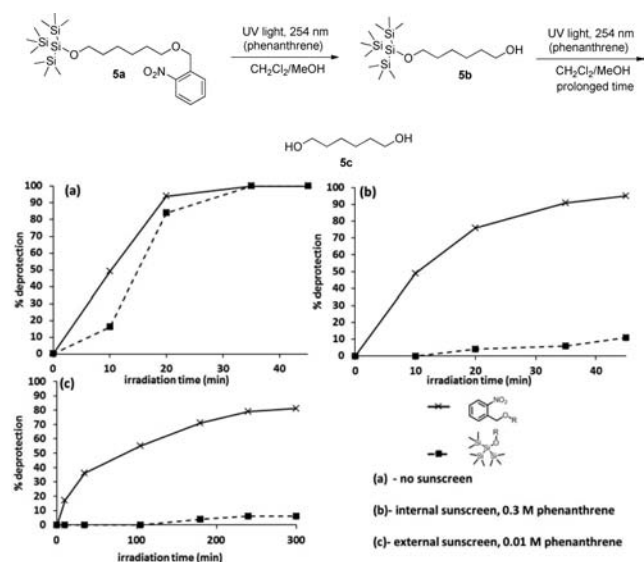


Figure 5. Selective intramolecular photodeprotection of 5a. Reaction conditions: 0.015 M of protected diol, 2 equiv of methanol-d₄, specified concentration of sunscreen in 1 mL of CD₂Cl₂, irradiated by 254 nm UV light. Deprotection conversions measured by ¹H NMR.

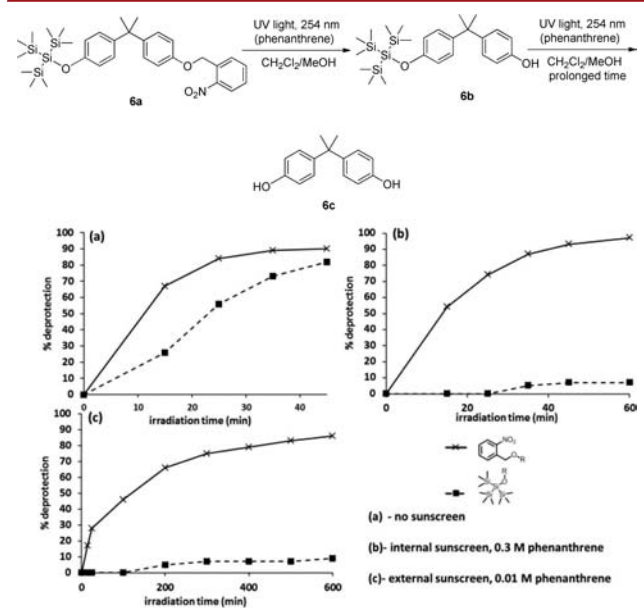


Figure 6. Selective intramolecular photodeprotection of 6a. Reaction conditions: 0.015 M of protected diol, 2 equiv of methanol-d₄, specified concentration of sunscreen in 1 mL of CD₂Cl₂, irradiated by 254 nm UV light. Deprotection conversions measured by ¹H NMR.

Finally, to emphasize the practicality of this method, a solution of 5a within a quartz NMR tube was introduced to a common polyethylene terephthalate (PET) bottle. PET absorbs UV light at the shortwave UV region²⁶ and should thus also allow for a selective deprotection as previously shown. Indeed, the use of a PET bottle gave excellent selectivity for the transformation of 5a to 5b (see Supporting Information) emphasizing the simplicity and practicality of this approach.

In conclusion, just as TMS ethers are more easily hydrolyzed than bulkier analogues, e.g. TBS, we show herein how photoremovable protecting groups may be selectively cleaved depending on their absorption coefficients. The use of a “sunscreen” molecule which absorbs light at the deprotection

wavelength was shown to efficiently modulate the photo-cleavage and achieve high selectivities with several protected alcohols. Moreover, the use of an external peripheral sunscreen, such as an external phenanthrene solution or even a simple PET bottle, allows for a straightforward method that does not necessitate additional purification schemes to remove the absorbing molecule added. Thus, a new concept that expands protecting group methodology is presented, where with a single light source selective deprotection may be achieved by choosing the appropriate protecting groups. The expansion of this concise methodology to improve existing chromatic orthogonal methods is currently being studied in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Additional data, experimental procedures, full characterization, and NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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