ORGANIC
LETTERS

2007
Vol. 9, No. 14
2649−2651

Isotope Effects in Photochemistry: Application to Chromatic Orthogonality

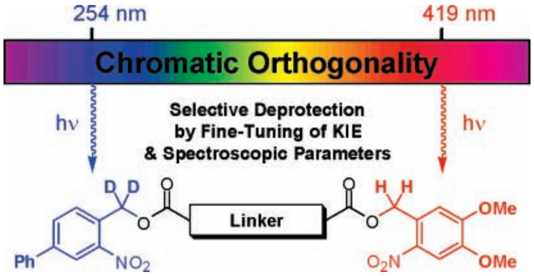
Aurélien Blanc and Christian G. Bochet*

Department of Chemistry, University of Fribourg, Chemin du Musée 9,
CH-1700 Fribourg, Switzerland

christian.bochet@unifr.ch

Received April 6, 2007

ABSTRACT



The main challenge in developing new wavelength-specific photolabile protecting groups is the rigorous control of the photolysis rate. This rate is controlled by two factors: the chromophore absorbance and the reaction quantum yield. Fine-tuning the properties by changing substituents or structural features is difficult, because both factors are independently affected. By the use of the kinetic isotope effect, we could tune the quantum yield without altering the absorbance, and hence control the overall reaction rate. We exemplified this approach with chromatically orthogonally protected diesters.

Orthogonality is the possibility of causing certain functional groups to react under a defined set of conditions without touching others.[1] In the specific case of photochemical reactions, we defined *chromatic orthogonality* as the possibility of transforming photochemically a specific chromophore at a specific wavelength, without affecting other photosensitive moieties.[2]

We were able to implement this strategy in the area of photolabile protecting groups[3] by exploiting the fact that different chromophores are excited at different energies.[4] Recently our own methodology was successfully applied to photolithography[5] and solid-phase peptide synthesis.[6] However, very limited success was initially obtained when different groups from the same structural family (e.g., *o*-nitrobenzyl alcohol derivatives) were used.[7] What makes it difficult to fine-tune the relative photochemical reaction rates of two chromophores[8] is that they depend on the chromophore's absorbances *and* the reaction quantum yield. Both parameters are influenced by substituent effects, frequently in an unpredictable way, and sometimes in opposite directions. Recently, a very interesting structure−reactivity relationship was identified on a limited number of substrates.[9] However, until more knowledge is collected on the interconnection between both parameters, we decided to tackle the problem using a different approach. We considered a photochemical reaction with a low quantum

---

[1] (a) Merrifield, R. B.; Barany, G.; Cosand, W. L.; Engelhard, M.; Mojsov, S. *Pept.*: *Proc. Am. Pept. Symp. 5th* **1977**, 488. (b) Schelhaas, M.; Waldmann, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 2056.

[2] Bochet, C. G. *Synlett* **2004**, 2268.

[3] For reviews see: (a) Amit, B.; Zehavi, U.; Patchornik, A. *Isr. J. Chem.* **1974**, *12*, 103. (b) Pillai, V. N. R. *Synthesis* **1980**, 1. (c) Pillai, V. N. R. *Org. Photochem.* **1987**, *9*, 225. (d) Bochet, C. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 125. (e) Pelliccioli, A. P.; Wirz, J. *Photochem. Photobiol. Sci.* **2002**, *1*, 441. (f) Falvey, D. E.; Sundararajan, C. *Photochem. Photobiol. Sci.* **2004**, *3*, 831.

[4] (a) Bochet, C. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 2071. (b) Blanc, A.; Bochet, C. G. *J. Org. Chem.* **2002**, *67*, 5567.

[5] del Campo, A.; Boss, D.; Spiess, H. W.; Jonas, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 4707.

[6] Kessler, M.; Glatthar, R.; Giese, B.; Bochet, C. G. *Org. Lett.* **2003**, *5*, 1179.

[7] Bochet, C. G. *Tetrahedron Lett.* **2000**, *41*, 6341.

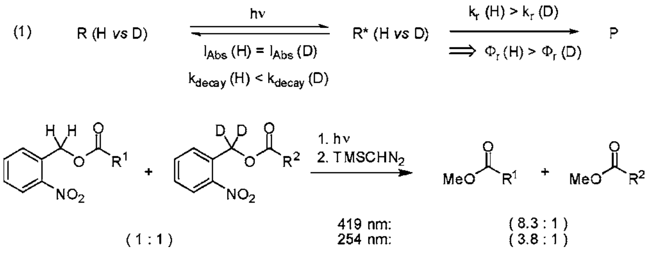
[8] By reaction rate, we imply the net observed rate at constant irradiation time, and not the rate of decay of an excited state.

[9] Katritzky, A. R.; Xu, Y. J.; Vakulenko, A. V.; Wilcox, A. L.; Bley, K. R. *J. Org. Chem.* **2003**, *68*, 9100.

10.1021/ol070820h CCC: $37.00

yield as a pre-equilibrium between the reactant and its excited state, fluorescence and/or nonradiative relaxation being the unproductive back-reaction. Hence, any event slowing down an irreversible subsequent process will de facto reduce the reaction quantum yield by favoring the back reaction (eq 1). This was experimentally achieved by exploiting the H/D kinetic isotope effect (KIE). On substrates from the *o*-nitrobenzyl family,[10,11] rate deceleration factors up to 8 were reached (Scheme 1).[12] In this work, we report on the application of this isotope effect to reach full chromatic orthogonality on bifunctional substrates.

Scheme 1. Group Differentiation Based on the KIE



Alcohols **1b**, **1d**, and **1f** were deuterated at the benzylic position by reduction of the corresponding acid chlorides (prepared in situ from the acid) or ketones with sodium borodeuteride in high yields (Table 1). It was important to avoid protic solvents and moisture during the sequence to ensure high isotopic purity.

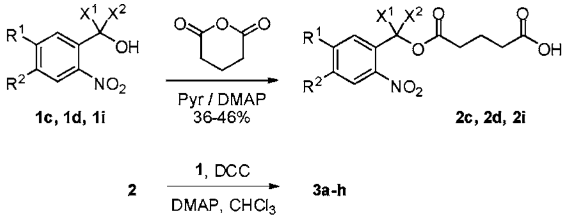
Table 1. Deuterated and Hydrogenated Photolabile Alcohols

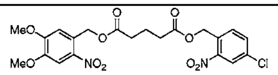
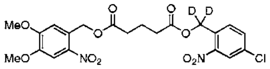
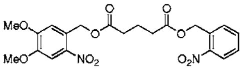
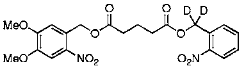
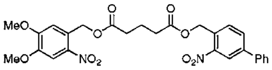
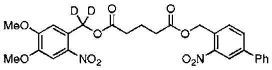
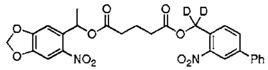
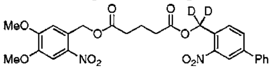
alcohol	R^1	R^2	X^1	X^2	yield (%)
1a[a]	H	H	H	H	
1b	H	H	D	D	94
1c[a]	OMe	OMe	H	H	
1d	OMe	OMe	D	D	93
1e	H	Cl	H	H	79
1f	H	Cl	D	D	65
1g[b]	H	Ph	H	H	83
1h[b]	H	Ph	D	D	71
1i	−OCH$_2$O−		Me	H	95

[a] Commercially available. [b] Obtained from alcohols **1e** and **1f** via Suzuki palladium cross coupling with phenylboronic acid.

The diesters **3a**−**h** were then prepared by first opening glutaric anhydride with 1 equiv of one of the alcohols **1c**, **1d**, and **1i**, followed by DCC-mediated esterification with alcohols **1a**,**b**,**e**−**h**. The yields were routinely higher than 70% (Table 2).

Table 2. Preparation of Photolabile Diesters



acid	alcohol	A[a]	ester	B[a]		yield
2c	**1e**				**3a**	76%
2c	**1f**				**3b**	87%
2c	**1a**				**3c**	94%
2c	**1b**				**3d**	69%
2c	**1g**				**3e**	71%
2d	**1g**				**3f**	93%
2i	**1h**				**3g**	76%
2c	**1h**				**3h**	89%

[a] A: "Western" terminus. B: "Eastern" terminus.

We were interested in the possibility of a real chromatic orthogonality, i.e., the deprotection of either terminus by choosing the appropriate wavelength (Figure 1; the diesters spectra are superimposable with the sum of the corresponding alcohols). To check this, we exposed the diesters **3a**−**h** to monochromatic light at 254 and 419 nm. Indeed, on the basis of previous results,[7] we know the rate of photolysis of hydrogenated protecting groups at these two wavelengths and that intermolecular energy transfer between two *o*-nitrobenzyl alcohol derivatives is minimal or does not exist. The results are summarized in Table 3.

As expected, the photolysis of the diesters **3b**,**d**,**g** at 419 nm gave predominantly the monoester with deprotection at the nondeuterated site (entries 2, 5, and 10), the KIE acting as a protection against photolysis, in contrast with protic diesters **3a**,**c** where no or poor selectivity was observed (entries 1 and 4). Knowing that the KIE was significantly reduced at shorter wavelength,[12] we then examined the

---

[10] (a) Barltrop, J. A.; Plant, P. J.; Schofield, P. *J. Chem. Soc., Chem. Commun.* **1966**, 822. (b) Patchornik, A.; Amit, B.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 6333. (c) Cameron, J. F.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4303. (d) Holmes, C. P.; Solas, D. W.; Kiangsoontra, B. PCT Int Appl. 9410128, 1994. (e) Pirrung, M. C.; Lee, Y. R.; Park, K.; Springer, J. B. *J. Org. Chem.* **1999**, *64*, 5042. (f) Blanc, A.; Bochet, C. G. *J. Org. Chem.* **2003**, *68*, 1138. (g) Specht, A.; Goeldner, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2008. (h) Gaplovsky, M.; Il'ichev, Y. V.; Kamdzhilov, Y.; Kombarova, S. V.; Mac, M.; Schwoerer, M. A.; Wirz, J. *Photochem. Photobiol. Sci.* **2005**, *4*, 33. (i) Lage Robles, J.; Bochet, C. G. *Org. Lett.* **2005**, *7*, 3545.

[11] For recent mechanistic studies see: (a) Corrie, J. E. T.; Barth, A.; Munasinghe, V. R. N.; Trentham, D. R.; Hutter, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 8546. (b) Il'ichev, Y. V. *J. Phys. Chem. A* **2003**, *107*, 10159. (c) Il'ichev, Y. V.; Schwoerer, M. A.; Wirz, J. *J. Am. Chem. Soc.* **2004**, *126*, 4581.

[12] Blanc, A.; Bochet, C. G. *J. Am. Chem. Soc.* **2004**, *126*, 7174.

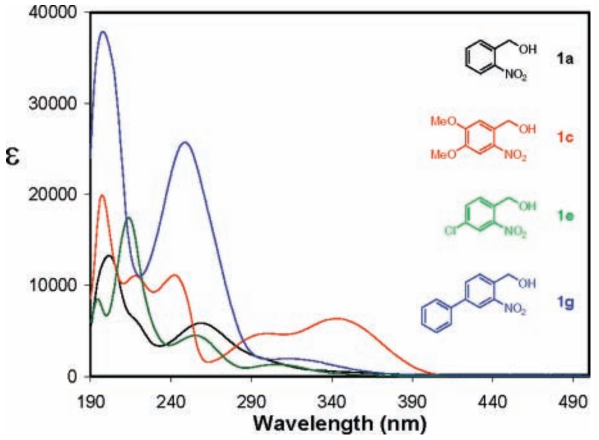
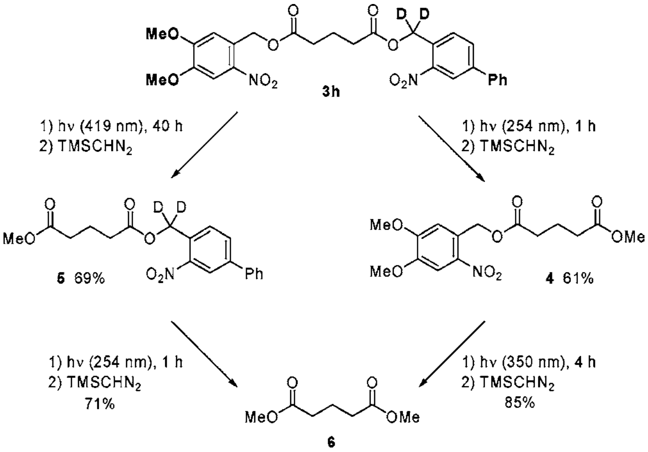


Figure 1. UV−vis spectra of photolabile groups in acetonitrile.

Scheme 2. Chromatic Orthogonality



photolysis results at 254 nm, an energy where we would expect little isotopic protection. Indeed, the optimization of spectroscopic (substituents) and kinetic parameters (H vs D) in the same direction should lead to the selectivity at only one wavelength. This was the case, the photolysis at high energy giving mainly a statistical deprotection of variously deprotected compounds (entries 3, 6, and 11). However, by carefully choosing a protecting group pair, such as in **3h** (entries 12 and 13), chromatic orthogonality was found (Scheme 2). Irradiation at 419 nm cleanly converted **3h** into **5** after $TMSCHN_2$ treatment with a yield of 69% and only 8% of the product of deprotection at the unwanted site (negative control gave lower selectivity, entry 7), whereas irradiation at 254 nm gave **4** with 61% and 13% of the other product. Further photolysis at the complementary wavelengths converted both **4** and **5** into glutaric diester **6**. This selectivity can be explained as follows: the 3,4-dimethoxy-6-nitrobenzyl group is known to yield products quite efficiently despite its very low quantum yield ($\Phi = 0.0013$)[13] because of its significant absorbance above 350 nm (Figure 1), whereas the 4-phenyl-6-nitrobenzyl group is highly reactive at 254 nm by both high quantum yield *and* absorbance.[7] A small reduction of Φ ($k_H/k_D = 3.6$ at 254 nm)[12] has no major impact on its relative rate with respect to the 3,4-dimethoxy-6-nitrobenzyl group (entries 8 and 9).

Table 3. Photolysis of Diesters with Monochromatic Light

				yield (%)			
entry	diester	λ (nm)	time (h)	A[a]	B[a]	C[a]	D[a]
1	**3a**	419	48	37	15	33	15
2	**3b**	419	48	**70**	5	8	17
3	**3b**	254	1	30	28	17	25
4	**3c**	419	48	55	12	5	28
5	**3d**	419	48	**85**	2		13
6	**3d**	254	1	25	22	20	33
7	**3e**	419	24	41	20	16	23
8	**3e**	254	1	5	**71**	11	13
9	**3f**	254	1	2	**78**	10	10
10	**3g**	419	10	**77**	4	5	14
11	**3g**	254	1	24	23	27	29
12	**3h**	419	40	**69**	8	6	17
13	**3h**	254	1	13	**61**	6	20

[a] A: Photolysis at the western terminus. B: Photolysis at the eastern terminus. C: Photolysis at both termini. D: Unreacted starting material. Yields measured spectroscopically after esterification with $TMSCHN_2$.

In conclusion, we were able to individually control the photolysis of two photolabile protecting groups by using monochromatic light. The two groups belong to the same family of chromophores, a feature that has precluded a real reactivity difference in the past. By exploiting the slower reactivity of the deuterated compounds, we could bring selectivity into the synthetically relevant range. The combination of a fine-tuning of these protecting groups and the currently established chromatic orthogonality to provide several orthogonal dimensions is currently underway.

Acknowledgment. The financial support of the Swiss National Science Foundation (grant 620-066063) is gratefully acknowledged.

Supporting Information Available: Selected experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070820H

---

(13) (a) Reichmanis, E.; Gooden, R.; Wilkins, C. W., Jr.; Schonhorn, H. *J. Polym. Sci., Polym. Chem. Ed.* **1983**, *21*, 1075. (b) Reichmanis, E.; Smith, B. C.; Gooden, R. *J. Polym. Sci., Polym. Chem. Ed.* **1985**, *23*, 1.