J|A|C|S COMMUNICATIONS

Published on Web 08/04/2010

Orthogonal Photocleavage of a Monochromophoric Linker

Laxminarayana Kammari, Tomáš Šolomek, Bokolombe Pitchou Ngoy, Dominik Heger, and Petr Klán*

Department of Chemistry, Faculty of Science, Masaryk University, Kamenice 5/A8, 625 00 Brno, Czech Republic

Received June 1, 2010; E-mail: klan@sci.muni.cz

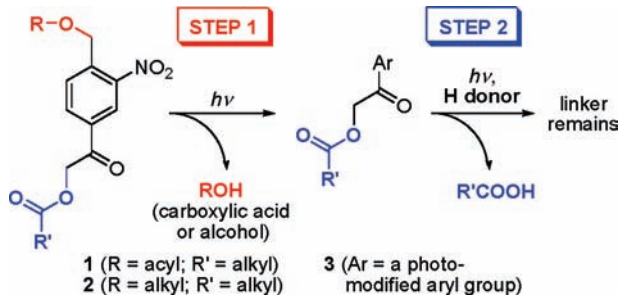
Abstract: The 4-acetyl-2-nitrobenzyl moiety, substituted in both benzylic and phenacyl positions with leaving groups, has been proposed as a monochromophoric photocleavable linker. The attached groups can be disconnected selectively and orthogonally upon irradiation.

Linkers or anchoring groups bind organic molecules to a support in solid-state synthesis, combinatorial chemistry, or drug delivery.[1,2] They should be stable under given conditions and disconnect selectively when required. Molecules are typically separated from the linker in such a way that the linker moiety remains attached to the support, which can be regenerated in a subsequent chemical step.[1] Photoinitiated ("reagentless") removal of a chromophoric linker is an attractive alternative, but the linker's photochemical properties must fulfill several criteria in order to allow rapid and efficient release. They are generally same as those required for photoremovable protecting groups (PPGs).[3−5] PPGs are inherently orthogonal[6] to non-photochemically removable protecting groups. Monochromatic light of different wavelengths has already been reported to differentiate photoreleases from multiprotected substrates.[7]

The aim of this work was to design a photocleavable monochromophoric linker connecting two molecules (or a support) through different functionalities, which can be disconnected selectively and orthogonally upon irradiation. Such an approach differs from that utilized with linkers that can be removed using a combination of photochemical and dark processes[1,2,8] or employing a bichromophoric system.[7,9] Here we report on a linker that combines the properties of two well-known photoremovable groups (2-nitrobenzyl and phenacyl) in a single chromophore. The work represents a pilot study; the design and synthesis of the new linker and some mechanistic considerations are presented here. To our knowledge, this work is the first successful attempt to use a *single chromophore* that possesses properties of a linker (or a *dual photoremovable protecting group*), from which the leaving groups (LG) can be sequentially released.

Strategy. The structure of the proposed *monochromophoric photocleavable linker* is based on a 4-acetyl-2-nitrobenzyl (ANB) moiety (**1** or **2**) substituted in both the benzylic and the phenacyl positions with carboxylic or alkoxy LGs (Scheme 1).

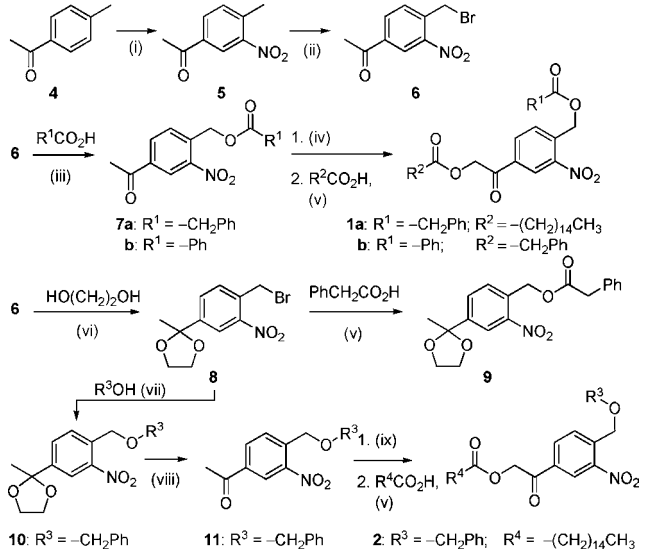
Scheme 1. Photochemistry of a Monochromophoric Linker



In step 1 (Scheme 1), the LG (RO^-) is released exclusively from the benzylic position by direct irradiation. This part of the ANB chromophore is essentially a 2-nitrobenzyl moiety, a well-established PPG, the photochemistry of which is based on a formal intramolecular 1,5-H shift in the primary reaction step, followed by complex transformations to give the liberated molecule.[10,11] At this point, "Ar" in **3** represents an unspecified chemically modified aromatic group. The second leaving moiety ($R'CO_2H$) in the phenacyl position of **3** is still protected and can be separated from the reaction mixture if required.

In step 2, $R'CO_2H$ is photochemically liberated in the presence of a hydrogen atom donor. An analogous reaction has been described for unsubstituted phenacyl groups which release the LGs from the α-position by initially abstracting hydrogen from another molecule.[12,13] This step is in fact a *safety-catch*[14] photoprocess, in which the protected substrate is released only by the simultaneous application of light and a chemical activator.[15] In the case that R′ is a solid support, step 2 is the support regeneration process.

Scheme 2. Synthesis of the ANB Derivatives[a]



[a] Reagents and conditions: (i) guanidinium nitrate, H_2SO_4, −5 °C; (ii) AIBN, NBS, CH_3CN, reflux; (iii) triethylamine (TEA), AcOEt (for **7a**) or NaI, DMF (for **7b**); (iv) Br_2, $CHCl_3$, 40 °C; (v) TEA, AcOEt; (vi) *p*-TsOH, benzene, reflux; (vii) aqueous NaOH, tetrabutylammonium hydrogen sulfate, CH_2Cl_2; (viii) I_2, acetone, 55 °C; (ix) Br_2, $CHCl_3$, 45 °C.

Synthesis of the ANB Derivatives. Compounds **1a**,**b** and **2** in Scheme 2 represent doubly substituted monochromophoric photocleavable ANB linkers. Compounds **7a** and **9**−**11** are model compounds used for the quantum yield measurements and other mechanistic investigations. The synthesis (see the Supporting Information) of **1** and **2** started with 4-methylacetophenone (**4**),

which was nitrated to give 4-methyl-3-nitroacetophenone (**5**) using nitroguanidine.[16] In the next several steps, both the benzylic and phenacyl positions were substituted with either carboxylate or alkoxy LGs. In the case of **1a**,**b**, the synthetic procedures included sequential bromination and nucleophilic displacement steps via the intermediates **6** and **7a**,**b** to give the target products with reasonable overall chemical yields (~25%). The preparation of **2** was carried out using similar steps; only the carbonyl group in **8** was protected as an acetal in the nucleophilic substitution reactions and subsequently released to give the synthetic precursor **11**. The overall chemical yield over six synthetic steps was ~7%. Compound **9** was prepared from **8** using a procedure similar to that described above.

Photolysis of the ANB Derivatives. To demonstrate that the ANB moiety is capable of orthogonal photochemical release of two different LGs, compounds **1a**,**b** and **2** were treated in the following manner:

For step 1 (Scheme 1), a degassed solution of the ANB linker (5×10^{-3} M) in acetonitrile was irradiated with a medium-pressure mercury lamp (450 W) through a Pyrex filter (>290 nm). When the starting material was consumed (>95%), the chemical yields (88−94%, Table 1) of the released acid (R^1CO_2H) or alcohol (R^3OH, Scheme 2) were determined using gas chromatography (GC). The acids were completely liberated from the esters **1a**,**b** in ~4 h, while the alcohol was released from the ether **2** in ~30 min under the given conditions. Only negligible amounts (<3%) of LG were released from the phenacyl position after prolonged irradiation.

Table 1. Chemical Yields of Leaving Groups Photorelease[a]

	yield (%) of [LG] release[b]	
linker	step 1[c]	step 2[c]
1a	88 [$PhCH_2CO_2H$]	90 [$CH_3(CH_2)_{14}CO_2H$]
1b	94 [$PhCO_2H$]	97 [$PhCH_2CO_2H$]
2	93 (91[d]) [$PhCH_2OH$]	90 (89[d]) [$CH_3(CH_2)_{14}CO_2H$]

[a] Degassed solutions (5×10^{-3} M) in acetonitrile were irradiated at λ > 290 nm to >95% conversion. All data are the average of at least three measurements. [b] The optimized acid (for **1a**,**b**; Scheme 2) or alcohol (for **2**) releases in the presence of 2-propanol (IPA; at least 2 mol equiv) as a H-atom donor (GC). [c] See Scheme 1. [d] In acetonitrile/methanol mixture (50:50, v/v).

For step 2, 2-propanol (IPA, a hydrogen atom donor) was added to the solution. The reaction mixture was then purged with argon and irradiated with the same light source as before. The chemical yields of acid ($R^2CO_2H = R^4CO_2H$, Scheme 2) release were 90−97% (GC). More than 2 mol equiv of IPA was needed to accomplish complete photorelease of the acid (Table 1). Higher amounts of the reagent did not improve the chemical yields but cut the irradiation time. For example, complete photorelease of phenylacetic acid from the intermediate **3**, formed from **1a**, in the presence of 1000 and 2 mol equiv of IPA was achieved in 11 and 50 h, respectively. The order of steps 1 and 2 cannot be reversed; both LGs are released from both **1** and **2** in the presence of a H-atom donor upon irradiation.

In the case of **2**, the initial concentration was kept equal to or below 5×10^{-3} M, because the released benzyl alcohol in step 1 acted as a hydrogen donor. In such a case, palmitic acid was partially released already in the first step; thus, a *safety-catch* obstacle was disabled. This observation was subsequently confirmed by a series of irradiation experiments using variable benzyl alcohol concentrations. The acyloxy substituent in the benzylic position of **1a**,**b** was found to undergo thermal hydrolysis in methanol to produce the corresponding methyl ester (~10% conversion in 24 h). Since it already presented an impediment, this solvent was not utilized for this particular study.

The side product, photochemically formed from the ANB moiety, has not been identified yet. However, the individual photorelease steps were studied on the model compounds **7a** and **9**−**11**.

Mechanism of Step 1. The 4-acetyl-2-nitrobenzyl derivatives **7a** (ester) and **11** (ether) and their acetal derivatives **9** and **10** were prepared to evaluate the acetyl group's influence on the photochemical behavior of the ANB moiety. Exhaustive irradiation of **7a** and **11** gave the corresponding acid and alcohol, respectively, in ~90% chemical yield (GC). The disappearance quantum yields (Φ) for the model compounds are listed in Table 2. Photodegradation of the esters was an order of magnitude less efficient than that of the ethers. The quantum yield was not determined for **7a** and **9** in methanol because the acyloxy substituent undergoes slow solvolysis in the dark, as in **1a**,**b**. Photodegradation of 2-nitrobenzyl esters has already been reported to be rather inefficient (Φ is usually below 0.1) compared to that of 2-nitrobenzyl ethers (Φ can reach 0.5 or more).[11,17−19] The quantum yields obtained in this work and listed in Table 2 are thus in agreement with this general tendency.

Table 2. Step 1: Quantum Yields of Disappearance (Φ)

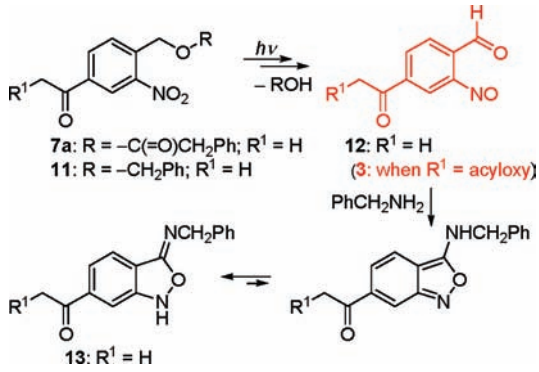
compound	Φ in CH_3CN[a]	Φ in CH_3OH[a]
7a (ketone)	0.051 ± 0.001	n.d.[b]
9 (acetal)	0.048 ± 0.001	n.d.[b]
11 (ketone)	0.88 ± 0.01	0.61 ± 0.02
10 (acetal)	0.77 ± 0.01	0.86 ± 0.02

[a] Degassed solutions (5×10^{-3} M) were irradiated at 313 ± 5 nm (optical bench). Φ was determined using a solution of 2-nitrobenzaldehyde in methanol ($\Phi = 0.41$) as an actinometer.[20] The irradiated solutions were analyzed using GC. Each sample was measured at least three times; the standard deviation of the mean is indicated. [b] n.d. = not determined. Esters **7a** and **9** in methanol were unstable in dark.

Intramolecular photoreduction of the nitro group and subsequent release of a leaving moiety from the benzylic position of the 2-nitrobenzyl chromophore has been systematically studied for the past 30 years.[3−5,10,11,21−24] A light-induced intramolecular 1,5-hydrogen shift in the primary chemical step to form *aci*-nitro intermediates, followed by formation of benzoxazolidines and subsequent ring opening to release the LG and give a 2-nitrosobenzaldehyde derivative, is a well-established mechanism. It has been reported that the triplet state ($^3n,\pi^*$) of 4-nitroacetophenone is formed rapidly upon irradiation[25] and that the reduction in the presence of H-atom donors occurs essentially on the nitro group instead of the acetyl group.[26,27] Therefore, we anticipated that the excited-state nature of the ANB group must be favorable for an intramolecular reduction of the NO_2 group and subsequent LG release, and that the intermediate **3** (Scheme 1) is a 2-nitrosobenzaldehyde derivative as shown in Scheme 3 (in red). Indeed, irradiation of **11** at 313 nm produced **12**, and its structure was established by its in situ reaction with benzylamine[28] to give the 3-(*N*-benzylamino)anthranil **13** in ~60% isolated chemical yield (Scheme 3). In the case of **7a**, the longer irradiation time caused extensive secondary decomposition of the reaction intermediate; the complex mixture of side products was not identified.

Mechanism of Step 2. The 2-nitrosobenzaldehyde **3** (or **12**) formed in step 1 (Scheme 3) possesses three functional groups which could potentially be photoactive. In the presence of hydrogen atom donors, aromatic ketones and aldehydes are known to be photoreduced to the corresponding alcohols or pinacols,[29−31] and aromatic nitroso compounds can give products of two- and four-

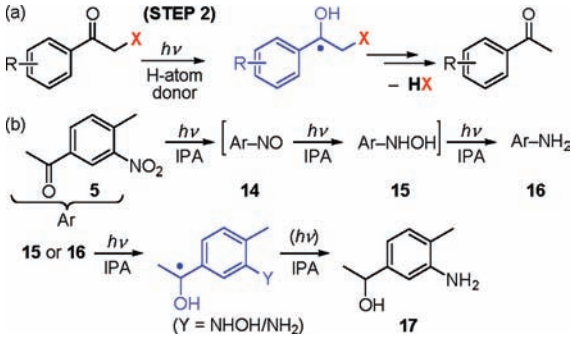
Scheme 3. A "Step 1" Photoproduct and Its Trapping



electron reduction (hydroxylamines and anilines, respectively).[31−33] Photorelease of a LG attached to the α-position of the phenacyl chromophore is known to be initiated by hydrogen abstraction by the triplet excited carbonyl group (Scheme 4a).[13,34] Therefore, we attempted to identify the intermediates responsible for LG release after **3** (Scheme 3) is photolyzed in the presence of 2-propanol.

Density functional theory quantum chemical calculations showed that the n,π^* triplet state of **12** is very low in energy (11 kcal mol^{-1}) and that excitation is largely located on the nitrosobenzene moiety, while the spin population resides on the nitroso group almost exclusively. Therefore, reduction of the nitroso group to the corresponding hydroxyamino derivative should be favored. Irradiation of the model compound 4-methyl-3-nitroacetophenone (**5**, 5×10^{-3} M) in acetonitrile in the presence of 10 molar excess of 2-propanol led to 4-methyl-3-aminoacetophenone (**16**) in ∼60% chemical yield; the reduction intermediates **14** and **15** were not trapped (Scheme 4b). Photoreduction of the acetyl group, closely related to the step 2 liberation of a LG, clearly did not occur until the later stages of this multistep process. The alcohol **17** was formed almost quantitatively after exhaustive irradiation. The chemical yields were evaluated from changes in the absorption spectra of the irradiated solutions (see the Supporting Information). Indeed, the quantum chemical calculations revealed that excitation in the triplet state of **15** and **16** is located preferentially on the carbonyl group, which makes it available for hydrogen abstraction. These results are in agreement with our experimental observation that more than 2 mol equiv of IPA was required for extensive acid photorelease in step 2, as well as with the fact that the photochemical efficiency of this reaction was rather low.

Scheme 4. Photoreduction of Acetophenone Derivatives



In conclusion, a new concept of a photocleavable monochromophoric linker was introduced in this work. The two LGs (a primary alcohol/carboxylic acid) of an ANB moiety can be disconnected selectively and orthogonally upon irradiation. The current limitations of the application are poor solubility of the system in aqueous solutions, mediocre yields of the protected chromophore preparation, the necessity to use UV radiation (<350 nm), and lower quantum efficiencies of the release in some cases. Several approaches for improving the monochromophoric linker properties and the mechanism of step 2 are currently under investigation in our laboratory.

Acknowledgment. This paper is dedicated to Prof. Richard S. Givens on the occasion of his 70th birthday. Support for this work was provided by the Grant Agency of the Czech Republic (203/09/0748), the Ministry of Education, Youth and Sports of the Czech Republic (MSM0021622413), and the European Union (CETOCOEN; CZ.1.05/2.1.00/01.0001). We thank J. Wirz for valuable comments and J. Frantisek (Ratiochem, Ltd., Brno) for mass spectrometric data. T.S. acknowledges the Scholarship for talented Ph.D. students of the Brno City.

Supporting Information Available: Experimental procedures, analytical data for all new compounds, and quantum chemical calculation results. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) James, I. W. *Tetrahedron* **1999**, *55*, 4855–4946.
(2) Backes, B. J.; Ellman, J. A. *Curr. Opin. Chem. Biol.* **1997**, *1*, 86–93.
(3) Bochet, C. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 125–142.
(4) Goeldner, M.; Givens, R. S. *Dynamic Studies in Biology*; Wiley-WCH: Weinheim, 2005.
(5) Pelliccioli, A. P.; Wirz, J. *Photochem. Photobiol. Sci.* **2002**, *1*, 441–458.
(6) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley-Interscience: New York, 1991.
(7) Bochet, C. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 2071–2073.
(8) Li, S. W.; Marthandan, N.; Bowerman, D.; Garner, H. R.; Kodadek, T. *Chem. Commun.* **2005**, 581–583.
(9) Kessler, M.; Glatthar, R.; Giese, B.; Bochet, C. G. *Org. Lett.* **2003**, *5*, 1179–1181.
(10) Schwörer, M.; Wirz, J. *Helv. Chim. Acta* **2001**, *84*, 1441–1458.
(11) Il'ichev, Y. V.; Schwörer, M. A.; Wirz, J. *J. Am. Chem. Soc.* **2004**, *126*, 4581–4595.
(12) Sheehan, J. C.; Umezawa, K. *J. Org. Chem.* **1973**, *38*, 3771–3774.
(13) Banerjee, A.; Falvey, D. E. *J. Am. Chem. Soc.* **1998**, *120*, 2965–2966.
(14) Kenner, G. W.; McDermot, J. R.; Sheppard, R. C. *J. Chem. Soc. D* **1971**, 636–637.
(15) Riguet, E.; Bochet, C. G. *Org. Lett.* **2007**, *9*, 5453–5456.
(16) Ramana, M. M. V.; Malik, S. S.; Parihar, J. A. *Tetrahedron Lett.* **2004**, *45*, 8681–8683.
(17) Bley, F.; Schaper, K.; Görner, H. *Photochem. Photobiol.* **2008**, *84*, 162–171.
(18) Yip, R. W.; Sharma, D. K.; Giasson, R.; Gravel, D. *J. Phys. Chem.* **1985**, *89*, 5328–5330.
(19) Sebej, P.; Solomek, T.; Hroudna, L.; Brancova, P.; Klan, P. *J. Org. Chem.* **2009**, *74*, 8647–8658.
(20) Galbavy, E. S.; Ram, K.; Anastasio, C. *J. Photochem. Photobiol. A-Chem.* **2010**, *209*, 186–192.
(21) Haag, R.; Wirz, J.; Wagner, P. J. *Helv. Chim. Acta* **1977**, *60*, 2595–607.
(22) Givens, R. S.; Conrad, P. G.; Yousef, A. L.; Lee, J.-I. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; Chapter 69, pp 1−46.
(23) Morrison, H. *Biological Applications of Photochemical Switches*; John Wiley and Sons, Inc.: New York, 1993; Vol. 2.
(24) Gaplovsky, M.; Il'ichev, Y. V.; Kamdzhilov, Y.; Kombarova, S. V.; Mac, M.; Schwörer, M. A.; Wirz, J. *Photochem. Photobiol. Sci.* **2005**, *4*, 33–42.
(25) Krishna, C. M.; Basu, S.; Roy, A. K. *J. Photochem. Photobiol. A* **1996**, *95*, 111–113.
(26) Pei, K. M.; Ma, Y. F.; Zheng, X. M.; Li, H. Y. *Chem. Phys. Lett.* **2007**, *437*, 153–158.
(27) Lin, Y. N.; Jeng, G. Y.; Chan, T. T.; Yen, G. F.; Wong, Y. G. *J. Chin. Chem. Soc.* **1998**, *45*, 313–318.
(28) Chen, L. J.; Burka, L. T. *Tetrahedron Lett.* **1998**, *39*, 5351–5354.
(29) Rubin, M. B. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Song, P.-S., Eds.; CRC Press: Boca Raton, FL, 1995; pp 437−448.
(30) Nau, W. M.; Pischel, U. In *Organic Photochemistry and Photophysics*; Ramamurthy, V., Schanze, K. S., Eds.; CRC Press: Boca Raton, FL, 2006; Vol. 14, pp 75−129.
(31) Klan, P.; Wirz, J. *Photochemistry of Organic Compounds: From Concepts to Practice*, 1st ed.; Wiley: Chichester, 2009.
(32) Döpp, D. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Song, P.-S., Eds.; CRC Press: Boca Raton, FL, 1995; pp 1019−1062.
(33) Hashimoto, S.; Kano, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 549–553.
(34) Banerjee, A.; Falvey, D. E. *J. Org. Chem.* **1997**, *62*, 6245–6251.

JA1047736