Facilitated photochemical cleavage of benzylic C–O bond. Application to photolabile hydroxyl-protecting group design†

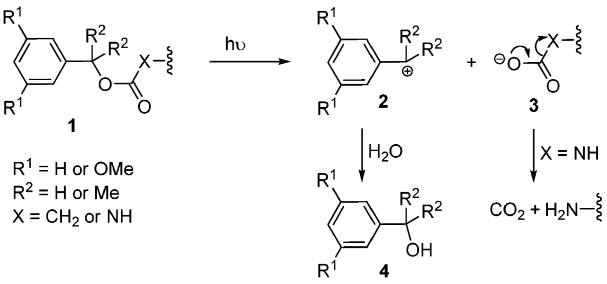
Pengfei Wang,* Lei Zhou, Xin Zhang and Xing Liang

Received (in Cambridge, UK) 21st October 2009, Accepted 4th December 2009
First published as an Advance Article on the web 23rd December 2009
DOI: 10.1039/b922021f

A new photolabile hydroxyl-protecting group has been developed by introducing a dimethylamino group to the meta position of an aromatic ring of the traditional trityl (Tr) protecting group.

Protecting groups are indispensable tools in organic chemistry. Among various protecting groups, photolabile protecting groups (PPGs) have valuable and unique features. They are typically removed under mild conditions by light without using any chemical reagents and are capable of releasing substrates in a spatially and temporally controlled manner.[1] These advantages are appealing to both basic and applied sciences such as organic chemistry, photolithography, and life sciences. In biophysics and biochemistry, there is increased attention on using the PPG method to probe biological events because it is an ideal way of releasing chemical compounds in a biological system with precise control.[2] In photolithography, light-induced removal of PPGs is a key step in the spatially addressable synthesis of oligonucleotides in the production of high-density DNA-chips for genomic analysis.[3] PPGs are also widely used for solid-phase synthesis as linkers.[4] While innovative applications continue to emerge,[5] development of new PPGs are highly sought.

Utilization of the photochemical cleavage of a benzylic C–O bond for PPG development can be dated back to the early 1960s.[6] Barltrop and Schofield first reported in 1962 that the *N*-benzyloxycarbonyl (Cbz) protected glycine in the form of **1** ($R^1 = R^2 = H$, and X = NH) underwent photochemical heterolysis to generate the benzylic cationic species **2** and the carbamate **3**. The former was trapped by water to provide the corresponding benzyl alcohol **4** and the latter would subsequently release glycine and carbon dioxide upon fragmentation (Scheme 1).

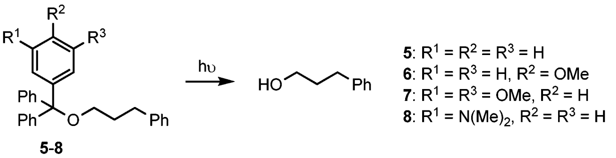


Scheme 1 PPGs featuring benzylic C–O bond cleavage.

Introduction of two methoxy groups at the meta positions (*i.e.* R^1 = OMe, and R^2 = H) of **1** greatly increased the chemical yields of released amino acids from heterolysis of the benzylic C–O bond.[6c] For instance, under the same irradiation conditions, photolysis of benzyloxycarbonyl–glycine only led to a 10% yield, while photo-deprotection of 3,5-dimethyoxybenzyloxycarbonylglycine had an 85% yield. This substituent effect was coined by Zimmerman as the excited state meta effect.[7] Later, Birr and co-workers introduced two methyl groups at the benzylic position of **1** (*i.e.* R^1 = OMe, and R^2 = Me, Scheme 1) to further stabilize the developing positive charge at the benzylic position in the transition state and to facilitate the C–O cleavage.[8] The modified protecting group (*i.e.* Ddz: α,α-dimethyl-3,5-dimethoxybenzyloxy) did become more photochemically reactive. However, the scope of these protecting groups is limited. They were used only for the release of good leaving groups such as a carbamate or carboxylate but not an alkoxide. The increased photochemical reactivity gained by introducing two methyl groups at the benzylic position (*i.e.* R^2 = Me) was at the cost of decreasing the stability of **1** under acidic conditions.[8]

We are interested in another way to facilitate the benzylic C–O bond cleavage by adding phenyl groups at the benzylic position (*i.e.* R^2 = Ph) to stabilize the positive charge in **2** (Scheme 1). By this means, photochemical release of alkoxide can be achieved.[9] We envision that the stability of the new protecting group under acidic conditions can be improved by proper substitution at the aromatic rings.

For proof of principle, we first examined the photochemical reactivity of the trityl (Tr) group which has been widely used in organic synthesis for the protection of hydroxyl groups.[10] Irradiation of trityl protected 3-phenylpropanol (**5**, $\varepsilon_{260\ \mathrm{nm}} = 1028\ \mathrm{M^{-1}\ cm^{-1}}$, Scheme 2) with a Vycor-filtered 450 W medium pressure mercury lamp ($\lambda > 210$ nm) resulted in release of 3-phenylpropanol from **5**. For 20 min irradiation in a 5 mM methanol solution, the ratio of 3-phenylpropanol to **5** was 1 : 10, determined by ^{1}H NMR analysis. Under the same conditions, 4-monomethoxytrityl (MMTr) protected 3-phenyl-propanol (**6**, $\varepsilon_{282\ \mathrm{nm}} = 1363\ \mathrm{M^{-1}\ cm^{-1}}$) achieved a 1 : 1 ratio of 3-phenylpropanol to **6**. In a control experiment,



Scheme 2 Photochemical reactivity of various triarylmethyl protecting groups.

---

901 14th Street South, Birmingham, Alabama, USA.
E-mail: wangp@uab.edu; Tel: +1 2059965625

† Electronic supplementary information (ESI) available: Experimental details, spectroscopic data and ^{1}H, ^{13}C spectra of **6**, **7**, **8**, **10**, **12a-d**, **13**, and **15**. See DOI: 10.1039/b922021f

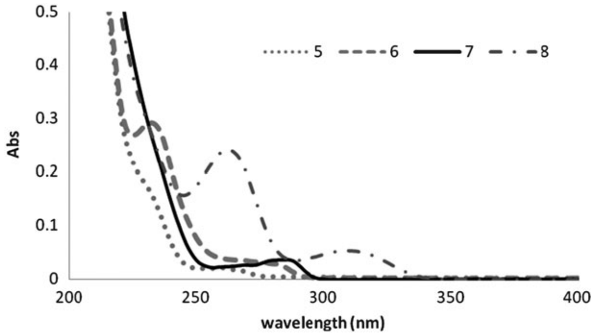
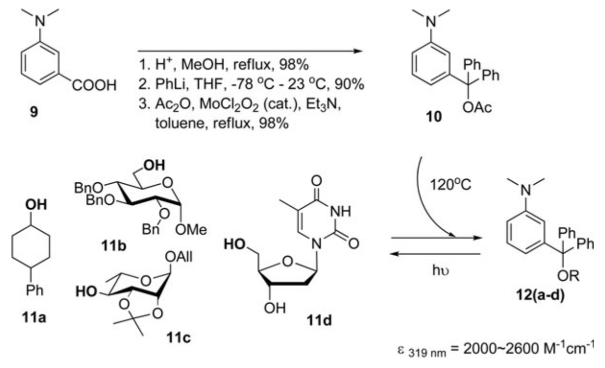


Fig. 1 UV spectra of compounds **5–8**.

the ether **6** did not decompose after 60 min at 50 °C without irradiation.

To improve the photochemical reactivity of the trityl type of protecting groups, we designed and prepared two meta substituted trityl groups. In **7**, two methoxy groups were added at the meta positions; in **8**, one meta dimethylamino group was used. The meta groups are expected to enhance the efficiency of photochemical cleavage of the benzylic C–O bond *via* the excited state meta effect. The UV profiles of **7** ($\varepsilon_{286\ \mathrm{nm}} = 1810\ \mathrm{M^{-1}\ cm^{-1}}$) and **8** ($\varepsilon_{309\ \mathrm{nm}} = 2662\ \mathrm{M^{-1}\ cm^{-1}}$) showed a bathochromic shift of the first absorption band, compared with that of **5** and **6** (Fig. 1, measured with $2\mathrm{x}10^{-5}$ M MeCN solutions). The quantum yields of releasing 3-phenylpropanol in acetonitrile/water (9 : 1) from **7** and **8** were 0.02 and 0.12, respectively.[11]

We then focused on the PPG in **8** (*i.e.* DMATr) as it has a higher quantum yield in releasing the alcohol, longer absorption wavelength, and enhanced stability toward acid treatment. The scope of DMATr as a new PPG was examined. The PPG reagent can be readily prepared from the commercially available dimethylamino-benzoic acid (**9**) in 86% yield over 3 simple steps (*i.e.* esterification with methanol, reduction with phenyl lithium, and acetylation with acetic anhydride catalyzed by $\mathrm{MoCl_2O_2}$[12]) (Scheme 3). Without using any other chemical reagents, simply heating **10** and the representative alcohols (**11a–d**) at 120 °C installed the PPG in high yields. It is worth noting that this protection reaction can be carried out under solvent-free conditions. In the case of protecting thymidine, a selectivity of *ca.* 4 : 1 between primary and secondary hydroxyl groups was achieved over 2 h heating. The isolated yield of mono-protection (at 5′-OH, **12d**) and di-protection (at both 3′- and 5′-OH, **12d′**) product was 79% and 18%, respectively. The selectivity gradually decreased afterwards, and full protection of both hydroxyl groups of thymidine was accomplished in 96% yield after 20 h (Table 1).



Scheme 3 Protection with DMATr.

Table 1 Protection and deprotection with DMATr

Entry	ROH	Protection yield (%)[a]	Deprotection yield (%)[c,d]	Irradiation time (min)
1	**11a**	92	87	15
2	**11b**	93	84[e]	35
3	**11c**	83	86[f]	30
4	**11d**	79[b]	81	60

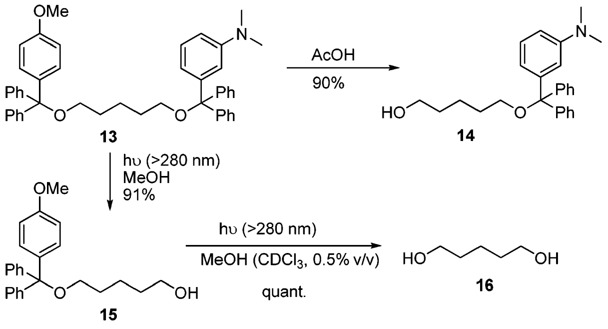
[a] ROH (0.1 mmol) and **10** (0.15-0.3 mmol) heated at 120 °C in a sealed tube in neat or with 50–100 μL of toluene. [b] Only the primary hydroxyl group was protected. [c] Irradiated with a 450 W medium-pressure mercury lamp equipped with a Pyrex filter sleeve without deaeration; the concentration of the reaction solutions ranging from 0.25 mM–5 mM in methanol unless indicated otherwise. [d] Isolated yields. [e] 5 mM in MeCN/H_2O (9 : 1), irradiated in a 10 mL Pyrex test tube. [f] 5 mM in methanol, irradiated in a 10 mL Pyrex test tube.

The photochemical reactions were conducted with a Pyrex-filtered 450 W medium pressure mercury lamp in a Hanovia reactor without deaeration. Small scale reactions were typically carried out in Pyrex NMR tubes with concentrations ranging from 5–10 mM in deuterated solvents. Preparative runs were in 250 mL reaction vessels with concentrations varied from 0.25–0.5 mM. The yields of the isolated alcohols were consistent with the NMR yields obtained by using internal references.

Although the photoreactions can be carried out in a variety of solvents,[13] methanol gave the best results. For example, irradiation of **12c** in methanol for 30 min led to **11c** in 86% yield, much higher than the 45% yield in acetonitrile/water (9 : 1). Alcohol **11a** was obtained in 87% yield from methanol after 15 min of irradiation, higher than the 74% yield from acetonitrile/water. The reaction of **12b** produced a high yield of **11b** (84%) even in acetonitrile/water after 30 min of irradiation. The photoreaction of **12d** is relatively slow, and it took 60 min to remove DMATr in 81% yield in methanol, higher than the 73% yield in acetonitrile/water.

The new DMATr group was expected to have enhanced stability toward acid treatment as compared with Tr and MMTr. Indeed, we observed that **8** remained intact upon treatment with formic acid in diethyl ether/methylene chloride (3 : 1) for 20 min. In contrast, the trityl group of **5** was completely removed under identical conditions. We attribute the increased stability of **8** to the electron-withdrawing inductive effect of the protonated meta dimethylamino group, which would disfavour formation of a benzylic cation like **2** *via* heterolysis of the C–O bond.

We prepared the compound **13**, equipped with the MMTr and DMATr in the same molecule, to examine orthogonality in deprotection of these two similar protecting groups (Scheme 4). Thus, the DMATr and MMTr were installed sequentially onto 1,5-pentanediol. Treatment of **13** with 80% acetic acid completely removed the MMTr group to generate the mono-protected alcohol **14** in 90% isolated yield. On the other hand, irradiation of **13** in methanol with Pyrex-filtered light ($\lambda > 280$ nm) for 15 min generated the alcohol **15** in 91% isolated yield.



Scheme 4 Controlled deprotection.

In the course of the photochemical studies, we observed that the traditional Tr and MMTr groups, which are inert to Pyrex-filtered irradiation ($\lambda > 280$ nm), can be photochemically removed with the Pyrex-filtered light in methanol if chloroform is present.[14] Presumably, HCl generated from the photoreaction of chloroform with a protic solvent promoted the removal of the protecting groups.[15] Thus, irradiation of **15** with Pyrex-filtered light in MeOH with 0.5% (v/v) $CDCl_3$ for 15 min led to a quantitative removal of the MMTr group to produce **16** based on ^{1}H NMR analysis (Scheme 4).[16]

In conclusion, a new PPG (*i.e.* DMATr) for the protection of alcohols has been developed. The PPG can be efficiently removed with light and has high stability toward acid treatment compared with traditional trityl type of protecting groups. A new protocol for PPG installation has also been developed. Primary and secondary alcohols can be protected in high yields. The photogenerated acid by irradiation of chloroform in a protic solvent proves to be an effective method in removing acid labile protecting groups, which will be useful in many important applications such as on-chip lithographic DNA synthesis,[17] photo-patterning organic conductive materials [18] and organic light-emitting materials.[19]

This work is supported by NSF (CHE-0848489) and the University of Alabama at Birmingham.

Notes and references

1 (*a*) V. N. R. Pillai, *Synthesis*, 1980, 1; (*b*) V. N. R. Pillai, *Org. Photochem.*, 1987, **9**, 225; (*c*) F. Guillier, D. Orain and M. Bradley, *Chem. Rev.*, 2000, **100**, 2091; (*d*) A. P. Pelliccioli and J. Wirz, *Photochem. Photobiol. Sci.*, 2002, **1**, 441.

2 (*a*) *Dynamic Studies in Biology*, ed. M. Goeldner and R. S. Givens, Wiley-VCH, Weinheim, Germany, 2005; (*b*) G. Mayer and A. Heckel, *Angew. Chem., Int. Ed.*, 2006, **45**, 4900.

3 (*a*) M. C. Pirrung, *Chem. Rev.*, 1997, **97**, 473; (*b*) S. P. A. Fodor, J. L. Read, M. C. Pirrung, L. Stryer, A. T. Lu and D. Solas, *Synthesis*, 1991, **251**, 767; (*c*) D. Woll, S. Walbert, K.-P. Stengele, R. Green, T. Albert, W. Pfleiderer and U. E. Steiner, *Nucleosides, Nucleotides Nucleic Acids*, 2003, **22**, 1395.

4 C. G. Bochet, *J. Chem. Soc., Perkin Trans. 1*, 2002, 125.

5 (*a*) M. Goard, G. Aakalu, O. D. Fedoryak, C. Quinonez, J. St. Julien, S. J. Poteet, E. M. Schuman and T. M. Dore, *Chem. Biol.*, 2005, **12**, 685; (*b*) K. N. Plunkett, A. Mohraz, R. T. Haasch, J. A. Lewis and J. S. Moore, *J. Am. Chem. Soc.*, 2005, **127**, 14574; (*c*) G. Han, C.-C. You, B.-J. Kim, R. S. Turingan, N. S. Forbes, C. T. Martin and V. M. Rotello, *Angew. Chem., Int. Ed.*, 2006, **45**, 3165; (*d*) M. A. Kostiainen, D. K. Smith and O. Ikkala, *Angew. Chem., Int. Ed.*, 2007, **46**, 7600; (*e*) D. D. Young and A. Deiters, *Angew. Chem., Int. Ed.*, 2007, **46**, 4290; (*f*) C. Park, J. Lim, M. Yun and C. Kim, *Angew. Chem., Int. Ed.*, 2008, **47**, 2959; (*g*) Y. Ohmuro-Matsuyama and Y. Tatsu, *Angew. Chem., Int. Ed.*, 2008, **47**, 7527; (*h*) T. Muraoka, C.-Y. Koh, H. Cui and S. I. Stupp, *Angew. Chem., Int. Ed.*, 2009, **48**, 5946.

6 (*a*) J. A. Barltrop and P. Schofield, *Tetrahedron Lett.*, 1962, 697; (*b*) J. A. Barltrop and P. Schofield, *J. Chem. Soc.*, 1965, 4758; (*c*) J. W. Chamberlin, *J. Org. Chem.*, 1966, **31**, 1658.

7 (*a*) H. E. Zimmerman and V. R. Sandel, *J. Am. Chem. Soc.*, 1963, **85**, 915; (*b*) H. E. Zimmerman and S. Somasekhara, *J. Am. Chem. Soc.*, 1963, **85**, 922; (*c*) H. E. Zimmerman, *J. Am. Chem. Soc.*, 1995, **117**, 8988; (*d*) H. E. Zimmerman, *J. Phys. Chem. A*, 1998, **102**, 5616.

8 C. Birr, W. Lochinger, G. Stahnke and P. Lang, *Liebigs Ann. Chem.*, 1972, **763**, 162.

9 (*a*) It is known that the 9-phenylxanthen-9-yl (pixyl) group and 9-phenylthioxanthyl (S-pixyl) are photochemically removable to release primary alcohols and nucleosides;[9b–c]; (*b*) A. Misetic and M. K. Boyd, *Tetrahedron Lett.*, 1998, **39**, 1653; (*c*) M. P. Coleman and M. K. Boyd, *J. Org. Chem.*, 2002, **67**, 7641.

10 *Protective Groups in Organic Synthesis*, ed. T. W. Greene and P. G. M. Wuts, Wiley-Interscience, New York, 1999.

11 (*a*) Quantum yields were determined by chemical actinometry. A. Defoin, R. Defoin-Straatmann, K. Hildenbrand, E. Bittersmann, D. Kreft and H. J. Kuhn, *J. Photochem.*, 1986, **33**, 237; (*b*) Monochromatic light was obtained by passing light from a 450 W medium pressure mercury lamp through three quartz cuvettes containing 2M $NiSO_4$ in 5% H_2SO_4 (cell 1), 0.8 M $CoSO_4$ in 5% H_2SO_4 (cell 2), and 2.46 E-4 M $BiCl_3$ in conc. HCl/H_2O (2 : 3) (cell 3). The monochromatic light centres at 285 nm and was opaque above 325 nm and below 250 nm[11c]; (*c*) H. E. Zimmerman, J. M. Nuss and A. W. Tantillo, *J. Org. Chem.*, 1988, **53**, 3792.

12 C.-T. Chen, J.-H. Kuo, V. D. Pawar, Y. S. Munot, S.-S. Weng, C.-H. Ku and C.-Y. Liu, *J. Org. Chem.*, 2005, **70**, 1188.

13 Photoreactions of **8** have been carried out in different solvents such as MeCN, MeCN/water, DMSO/water, acetone/water, benzene/water, chloroform, chloroform/water, and methanol. The reactions in methanol and MeCN/water (9 : 1) seemed to provide better results.

14 Irradiation of **6** in MeOH (5 mM) with 0.5% (v/v) chloroform for 20 min with the Pyrex-filtered light resulted in complete removal of the MMTr group. Under the same reaction conditions, the Tr group could not be removed from **5**, even after increasing chloroform in methanol to 10%. However, deprotection of Tr was observed after 20 min irradiation with a 3-phenylpropanol/5 ratio of 0.06 : 1 in MeOH/chloroform (1 : 1) and 0.15 : 1 in MeOH/chloroform (1 : 9). When these irradiated reaction solutions were kept in dark, the deprotection reactions gradually reached completion overnight, which clearly indicates the existance of photogenerated acidic substance(s) catalyzing the reactions. Furthermore, in control experiments, there was no sign of photoreactions when **5** and **6** were irradiated with the Pyrex-filtered light in MeOH, MeCN/water, chloroform, or MeCN/chloroform.

15 (*a*) Utilization of photogenerated acids from sensitizers in protecting group installation have been recently reported, albeit the identity of some acids are not clear;[15b–c]; (*b*) H. J. P. de Lijser and C.-K. Tsai, *J. Org. Chem.*, 2004, **69**, 3057; (*c*) R. P. Oates and P. B. Jones, *J. Org. Chem.*, 2008, **73**, 4743.

16 See details in Supporting Information.

17 X. Gao, P. Yu, E. LeProust, L. Sonigo, J. P. Pellois and H. Zhang, *J. Am. Chem. Soc.*, 1998, **120**, 12698.

18 (*a*) C. W. Lee, Y. H. Seo and S. H. Lee, *Macromolecules*, 2004, **37**, 4070; (*b*) J. F. Yu, M. Abley, C. Yang and S. Holdcroft, *Chem. Commun.*, 1998, 1503.

19 (*a*) C. D. Muller, A. Falcou, N. Reckefuss, M. Rojahn, V. Wiederhim, P. Rudati, H. Frohne, O. Nuyken, H. Becker and K. Meerholz, *Nature*, 2003, **421**, 829; (*b*) J. V. Crivello, R. Falk and M. R. Zonca, *J. Polym. Sci., Part A: Polym. Chem.*, 2004, **42**, 1630.