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## **Development of hydrophilic photolabile hydroxyl protecting groups**†‡

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Hydrophilic photolabile protecting groups (PPGs) for hydroxyl protection have been developed. The new PPGs are derived from 3-(dimethylamino)trityl (DMATr) by replacing the two methyl groups with two hydrophilic butyryl groups. The new PPG reagents can be readily prepared and installed. They are stable in the dark but can be removed cleanly and efficiently in aqueous environments upon irradiation with a UV lamp or sunlight.

Photolabile protecting groups (PPGs) are protecting groups that can be removed with photo irradiation. They are indispensable tools in a broad spectrum of basic and applied research areas.<sup>1–5</sup> Their advantages stem from using light as a traceless reagent in the removal process. Photochemical removal of protecting groups often occurs under mild conditions and does not require chemical reagents. In addition, light also provides precise temporal and spatial control over the course of a reaction. Numerous efforts have been devoted to developing new PPGs.<sup>1,4</sup> However, ever increasing interests in utilizing a light-controlled approach in a broad range of research fields have spurred increasing demands for the further development of current and new PPGs.

We are interested in developing structurally simple and mechanistically novel PPGs with different chemical/photochemical properties for various applications. We have recently reported a series of new PPGs, featuring a salicyl alcohol skeleton, which can be used for carbonyl protection.<sup>6</sup> We hypothesize that the effective and efficient photolysis of the carbonyl PPGs starts from the heterolytic cleavage of the benzylic C–O bond. Based on this assumption, we inferred that the structurally related triarylmethyl groups could be robust PPGs for hydroxyl groups. Research along this direction produced useful results. For example, heating an alcohol (1) with the PPG reagent 2 at 120 °C smoothly installed the dimethylamino trityl PPG (*i.e.* DMATr) to produce the ether 3 in high yield (Scheme 1). Upon irradiation, the alcohol was released in high efficiency.<sup>7</sup>

One important aspect of PPG applications is in bio-related research as so-called "photocages", where the photochemical removal of the photocages often takes place in aqueous environments. Since the substrates to be caged are often polar biological



Scheme 1 Photolabile hydroxyl protecting group DMATr.

molecules and a low concentration of the caged compound is sufficient, the caged substrate can have meaningful solubility in water even if the photocage itself is hydrophobic. However, when a relatively high concentration of caged compounds is needed, especially when the substrate to be caged is not polar enough,<sup>8</sup> increasing the water-solubility of the caged substrate will rely on improving the hydrophilicity of the PPG segment. The hydrophobic nature of DMATr obstructs its wide applications in aqueous environments. Herein we report our effort in modifying DMATr to improve its water solubility.

We found that the new trityl PPG in the ether **4** proved to be a robust hydroxyl PPG for releasing alcohols in aqueous solutions under neutral or basic conditions (Scheme 2).





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<sup>&</sup>lt;sup>†</sup>This paper is part of a themed issue on photoremovable protecting groups: development and applications.

<sup>&</sup>lt;sup>‡</sup> Electronic supplementary information (ESI) available: experimental details, spectroscopic data, UV spectra of 4a, and <sup>1</sup>H and <sup>13</sup>C NMR spectra of 4a, 7a–7e, 8, 9, 11, 12, and 17–22, and HPLC profiles of the reaction of 4a. See DOI: 10.1039/c1pp05281k

Table 1 Hydrophilic photolabile hydroxyl protecting group

Entry	R'OH (10)	Yield of $7^a$ (%)	4	Yield of $5/6^{c,d}$ (%)	Irradiation time (min)
1	Aco Aco Aco Me	79	PPG-O HO HO OH OMe	96/93 <sup>f</sup> 96/92	12 <sup>r</sup> 12
2	10a O(CH <sub>2</sub> ) <sub>3</sub> OH AcO OAc	83	4a O(CH <sub>2</sub> ) <sub>3</sub> O-PPG HO HO HO OH	97/93	10
3	10b но ОН	42 <sup>b</sup>	4b РРС О ОН ОН	99/96	10
4	10c AcHN O HO-OMe	97	AcHN O O OK PPG	95/96	10
5		81	4d PPG O O O O O O O	100/95	10
	10e		4e		

<sup>*a*</sup> Protection reactions were completed by heating 1.5 equiv. of the PPG reagent (3 equiv. for **10a**) and 1 equiv. of R'OH at 120 °C. <sup>*b*</sup> The reaction was carried out with 1 equiv. of the PPG reagent and 6 equiv. of the alcohol. <sup>*c*</sup> Reactions were carried out in 3 mM aqueous solutions of **4** under basic conditions without deaeration. <sup>*d*</sup> Yields were determined by <sup>1</sup>H NMR with an internal reference. <sup>*e*</sup> Irradiation with a 450 W medium pressure mercury lamp equipped with a Pyrex filter sleeve. <sup>*f*</sup> Reaction was carried out in 3 mM aqueous solutions of purified **4** under neutral conditions without deaeration.

For example, a quantum yield of 0.23 was obtained in releasing methyl  $\alpha$ -D-glucoside (5a) from the purified ether 4a  $(\varepsilon_{\rm H_2O, 315 nm} = 1.7 \times 10^3 \,\mathrm{M^{-1} \, cm^{-1}})$  in water without deaeration.<sup>9</sup> The chemical yields of 5a and 6 after irradiation of a 3 mM aqueous solution (pH  $\sim$  7) with a 450 W medium pressure mercury lamp filtered through a Pyrex sleeve for 12 min were 96% and 93%, respectively, based on <sup>1</sup>H NMR analysis. Alternatively, the ether 7 was hydrolyzed, and without purification, the residue obtained after the removal of methanol was re-dissolved in water. The resulting basic solution (pH  $\sim$  12) was irradiated under the same conditions and provided similar results, i.e., the chemical yields of 5a and 6 by NMR were 96% and 92%, respectively (Table 1, entry 1). The yields were further confirmed in a preparative run. To simplify column purification, the dicarboxylate 6 was treated with diazomethane and isolated as its corresponding dimethyl ester 8 in 92% yield. A trace amount of a byproduct 9 (<2%) was also isolated. The structures of 8 and 9 differed in the substitution of the *meta* amino group: where compound 9 has only one 4-butyryl chain connected to the nitrogen. The structure of 9 was confirmed by its independent synthesis.

Removal of the PPG DMATr in methanol or water often led to multiple products derived from the PPG chromophore;<sup>7</sup> however, the new PPG provided much cleaner reactions with excellent recovery yields of the PPG reagent. For example, LC-MS

analysis of the crude reaction mixture **4a** (pH ~ 12) did not show significant byproducts (see ESI<sup>‡</sup>). Irradiation of **4a** for 12 min and 20 min did not cause a perceptible change in the reaction outcomes based on NMR and HPLC analysis (for HPLC profiles, see ESI<sup>‡</sup>). Encouraged by these results, we examined the photo release of some representative compounds, where consistent results were obtained (Table 1, entries 2–5). Photoreactions proved to be clean with irradiation by both a mercury lamp and sunlight. For example, the reaction of **4d** (3 mM aqueous solution) under sunlight resulted in clean deprotection after 80 min. It is interesting to note that with continuous irradiation under sunlight for 7 h, slow decomposition of the PPG reagent became detectable.

It has been demonstrated that DMATr is relatively stable towards acid treatment, and constitutes orthogonal protecting groups with the conventional acid-labile trityl type protecting groups.<sup>7</sup> As expected, the new PPG in **4** also showed remarkable stability under acidic conditions. For example, treatment of **4a** and its corresponding Tr counterpart with HCOOH/Et<sub>2</sub>O/dichloromethane (2:3:1) for *ca*. 1 h resulted in the complete removal of the Tr group in methyl 6-*O*-trityl- $\alpha$ -D-glucoside; however, there was no detectable decomposition of **4a** by NMR and TLC.

We further synthesized two other protected alcohols, *i.e.* **11** and **12** equipped with similar PPGs (Scheme 3). Under the same



Scheme 3 Similar PPGs.

conditions of saponification and irradiation in water, 11 and 12 showed results similar to that of 7d, except that the reaction of 11 produced a minor byproduct derived from the PPG moiety upon inspection of the crude reaction mixture by NMR spectroscopy. Interestingly, the reactions of 11 appeared to be slower than the others when the photoreactions of 7d, 11 and 12 were carried out in MeCN/water (9:1) or methanol after saponification. In addition, the reactions in these solvents became less clean than in wholly aqueous solution.

Synthesis of the PPG reagents is straightforward (Scheme 4). From the commercially available 3-amino benzoic acid 16, the trityl alcohol 17 was obtained after a sequence of esterification, acetylation of the amino group, addition of phenyl groups to the methyl ester moiety, and removal of the acetyl group under alkali conditions. Alkylation of the amino group of 17 with bromo esters led to 18 and 8. Conjugate addition of 17 to methyl acrylate led to 19. Subsequent acetylation with acetic anhydride catalyzed by MoCl<sub>2</sub>O<sub>2</sub> converted the trityl alcohols 18, 19, and 8 to the corresponding PPG reagents 20, 21, and 22, respectively.<sup>10</sup> The neutral protecting group installation protocol developed in our laboratory<sup>7</sup> was successfully generalized to the new reagents. Thus, without using any other chemical reagents, heating the trityl acetates and an alcohol R'OH at 120 °C resulted in 7, 11, and 12, respectively. In the reaction to form 7a, a relatively high 22/10a ratio (i.e. 3:1) was needed due to the undesired acetyl migration confirmed when heating 10a (Table 1, entry 1). In the reaction of 10c with 22, glycerol was used in excess (Table 1, entry 3). The low combined yields of 7c (42%) and the di-protected byproduct (22%) were due to the presence of water in glycerol, and the corresponding trityl alcohol 8 was obtained as another byproduct. In the reaction of 10e, the di-protected thymidine was isolated as a byproduct in 18% yield





(Table 1, entry 5). Subsequent saponification of 7, 11, and 12 provided the water-soluble caged compounds.

## Conclusions

In conclusion, we converted the robust DMATr PPG to its watersoluble counterparts. The new PPGs led to efficient and clean photo-deprotection reactions in aqueous environments. The new PPG reagents can be readily prepared, and the PPG installation can be conveniently achieved by using the neutral protection protocol. We anticipate the new PPGs can be useful in a wide range of research.

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