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Structurally Simple Benzylidene-Type Photolabile Diol Protecting Groups

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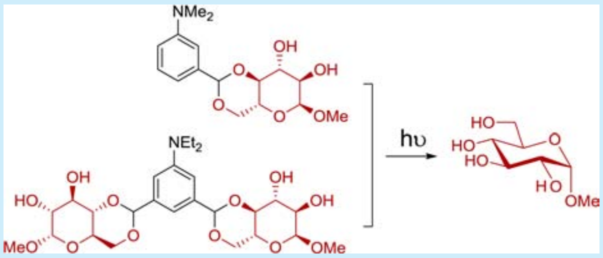
Supporting Information

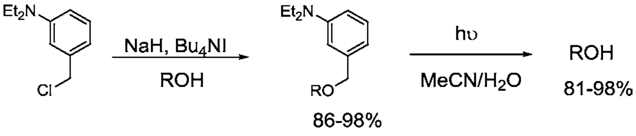
ABSTRACT: Two structurally simple photolabile protecting groups for releasing 1,2- and 1,3-diols have been developed. The diols can be protected in high yields and released from their corresponding acetals with high chemical efficiency.



Protecting groups are indispensable tools in organic chemistry. 1,2- or 1,3-diols are often protected as their respective 1,3-dioxolanes or 1,3-dioxanes.[1] These cyclic acetals can be converted back to the parent diols under various chemical conditions such as acidic treatment or hydrogenolysis. Photochemical deprotection is deemed unique in that it can avoid using any other chemical reagents and the reaction conditions are typically mild.[2−5] Moreover, photochemical release of a functional group has high temporal and spatial precision, which is attractive to research in biochemistry, neurobiology, photolithography, and materials science.[6−10] However, photolabile protecting groups (PPGs) for 1,2- and 1,3-diol protection are rare. The 2-nitrobenzylidene PPG, based on the well-established 2-nitrobenzyl PPG photochemistry, was the first PPG studied for release of diols.[11−16] However, it only photochemically releases one of the two protected hydroxyl groups and requires a thermal hydrolysis step to free the second hydroxyl group. Recently, 6-bromo-7-hydroxy-4-formylcoumarin,[17] 8-bromo-7-hydroxyquinoline,[18] salicylaldehyde derivatives,[19] and 2-acetonaphthone[20] have been explored for diol protection.

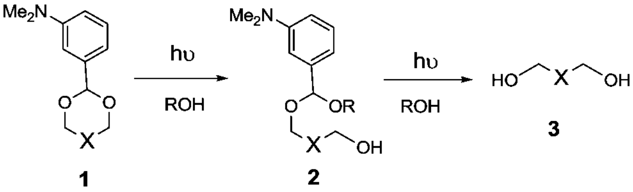
We recently demonstrated that the 3-diethylaminobenzyl group (DEABn) is a robust hydroxyl PPG; it releases various alcohols (including primary, secondary, and tertiary alcohols) by cleavage of the benzylic C−O bond effectively (Scheme 1).[21] The design of DEABn is based on the excited-state *meta* effect.[22−25] It is also known that *m*-dimethylamino group(s) can facilitate benzylic C−O bond cleavage to release diazeniumdiolates[26] and carboxylic acids.[27]

Scheme 1. DEABn Hydroxyl PPG



Encouraged by the results for DEABn, we designed a structurally simple and photocleavable new benzylidene-type diol PPG derived from the DEABn hydroxyl PPG (Scheme 2).

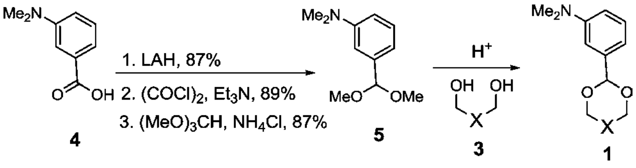
Scheme 2. Design of the New Diol PPG



We expected that irradiation of acetal **1** would cleave the benzylic C−O bond as occurred in the removal of the DEABn PPG (Scheme 1).[28] In a protic solvent, intermediate **2** would form, and irradiation would continue to break benzylic C−O bonds and eventually lead to release of diol **3**. Thus, unlike the 2-nitrobenzylidene PPG, release of diol with this new PPG would not require a thermal hydrolysis step catalyzed by either an acid or a base.

The PPG reagent was readily synthesized from commercially available 3-(dimethylamino)benzoic acid (**4**) (Scheme 3). Its reduction with lithium aluminum hydride (LAH) followed by

Scheme 3. Synthesis of the PPG Reagent and PPG Installation



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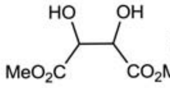
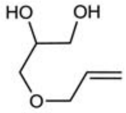
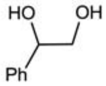
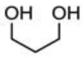
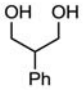
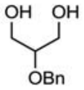
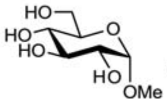
Swern oxidation[29] of the resulting benzyl alcohol led to the corresponding benzaldehyde, which was then converted to dimethyl acetal **5**. The reaction of PPG reagent **5** with various diols **3a−g** resulted in the photolabile acetals **1a−g** in high yields (Table 1). In the cases of diols **3c**, **3e**, and **3f**, the respective acetals were obtained as mixtures of two diastereomers.

Table 1. Installation of the New PPG and Release of Diols

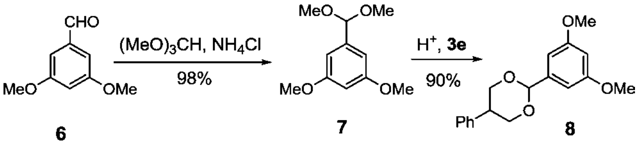
entry	Diol (3)	protection yield (%)	deprotection yield (%)[d,e]
1	 **3a**	**1a**: 71[a]	74
2	 **3b**	**1b**: 87[b]	81[f]
3	 **3c**	**1c**: 94[b]	78
4	 **3d**	**1d**: 89[b]	74
5	 **3e**	**1e**: 85[b]	89
6	 **3f**	**1f**: 91[a]	81
7	 **3g**	**1g**: 85[c]	94

[a] Diol **3**, PPG reagent **5**, and camphorsulfonic acid (CAS) in toluene at 100−120 °C. [b] Diol **3**, PPG reagent **5**, and CAS in chloroform at 66 °C. [c] Diol **3**, PPG reagent **5**, and CAS in DMF at 66 °C. [d] A 5.0 mM solution in methanol in 5 mm NMR tubes was irradiated for 30 min with a 450 W medium-pressure mercury lamp equipped with a Pyrex filter sleeve ($\lambda > 300$ nm) without deaeration. [e] Isolated yields. [f] Isolated after derivatization.

Photolysis of acetals **1a−g** in methanol released the corresponding diols smoothly in good yields (Table 1). For instance, irradiation of **1d** (5.0 mM in CD_3OD) for 30 min with a 450 W medium-pressure mercury lamp equipped with a Pyrex filter sleeve ($\lambda > 300$ nm) without deaeration led to complete conversion of **1d**. The yield of the released diol **3d** reached 82% based on ^1H NMR analysis. In a larger-scale run (5.0 mM in CH_3OH in multiple NMR tubes) under the same irradiation conditions, the released **3d** was isolated in 74% yield. The PPG was also able to protect monosaccharide **3g** in the form of acetal **1g** ($\varepsilon_{(MeOH)308\ nm} = 2500\ M^{-1}\ cm^{-1}$, $\Phi = 0.08$) in high yield and release it in 94% yield (Table 1, entry 7). The photoreactions can also take place in acetonitrile/water but with lower efficiency. It is worth noting that unlike the benzylidene-type diol PPGs obtained from 6-bromo-7-hydroxy-4-formylcoumarin[17] and salicylaldehyde,[19] which show either complete resistance to releasing 1,3-diols or notably lower efficiency in releasing 1,3-diols than releasing 1,2-diols, the new diol PPG releases both 1,2- and 1,3-diols efficiently. Moreover, the acetals are stable neat or in organic solutions. For example, in a control experiment, a solution of **1b** (5 mM in CD_3OD) was kept at 50 °C for 1 h, and no thermal decomposition could be detected by ^1H NMR analysis.

We recently demonstrated that the DEABn PPG differs from the known 3,5-dimethoxybenzyl (DMBn) PPG, which was also based on the *meta* effect.[30] The latter releases only good leaving groups such as carboxylate, carbonate, and carbamate. Herein we also compared the 3-dimethylaminobenzylidene and 3,5-dimethoxybenzylidene chromophores in releasing diols. Thus, the commercially available 3,5-dimethoxybenzaldehyde (**6**) was converted to the corresponding acetal **7** (Scheme 4). Its reaction with diol **3e** afforded dioxane **8** ($\varepsilon_{(MeOH)282\ nm} = 2600\ M^{-1}\ cm^{-1}$). UV spectra of **1e** and **8** revealed a bathochromic shift of **1e** compared with **8** (Figure 1).

Scheme 4. Synthesis of Dioxane 8



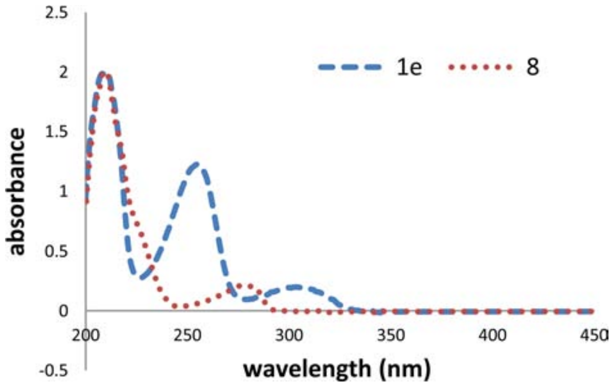
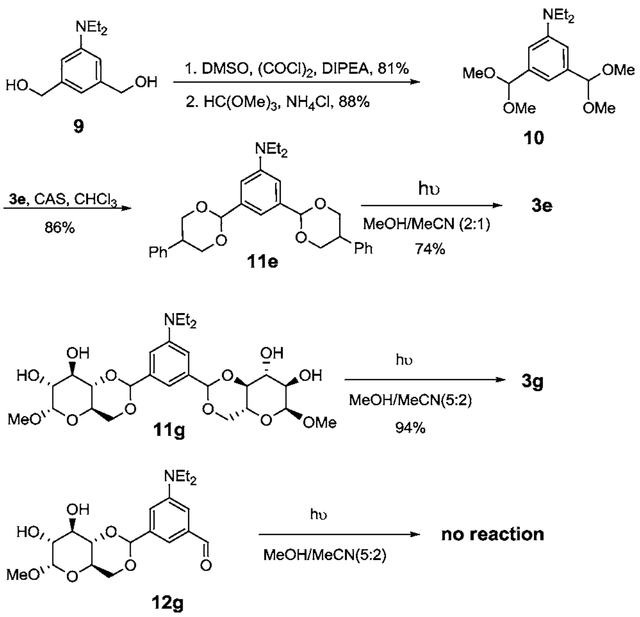


Figure 1. UV−vis spectra of **1e** and **8**.

Irradiation of **8** for 30 min (with either a Pyrex filter sleeve ($\lambda > 300$ nm) or a Vycor filter sleeve ($\lambda > 220$ nm)) could not release diol **3e**, while dioxane **1e** ($\varepsilon_{(MeOH)304\ nm} = 2500\ M^{-1}\ cm^{-1}$) released the diol in 89% yield ($\lambda > 300$ nm) (Table 1, entry 5). These results confirmed again that one *m*-amino group is more powerful than two *m*-methoxy groups in facilitating the benzylic C−O cleavage, consistent with the different reactivities of DEABn and DMBn observed in releasing alcohols.[21]

One advantage of the new diol PPG is that photolysis of the new PPG does not change the PPG's working chromophore, in contrast to the 2-nitrobenzyl series of PPGs. We thus designed a diol PPG that releases two diols from one chromophore. As shown in Scheme 5, from diol **9**, two steps led to diacetal **10**. It protected diol **3e** to provide diacetal **11e** in 86% yield. Irradiation of **11e** (5.0 mM in 2:1 MeOH/MeCN) for 30 min released **3e** in 74% yield. Diacetal **11g** ($\varepsilon_{(MeOH)318\ nm} = 3400\ M^{-1}\ cm^{-1}$, $\Phi = 0.07$) was also prepared using the same procedure. Its irradiation (5.0 mM in 5:2 MeOH/MeCN) for 30 min released methyl glucoside **3g** cleanly in 94% yield. However, the aldehyde **12g**, isolated as a byproduct from the reaction to prepare **11g**, was inert under the irradiation

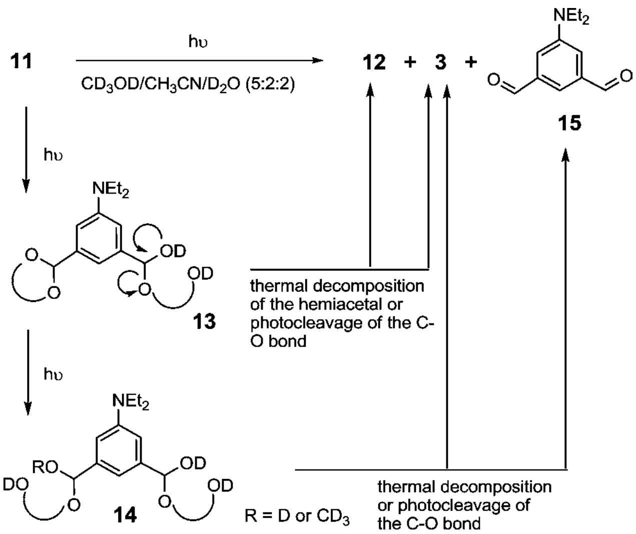
Scheme 5. Release of Two Diols from One PPG Chromophore



conditions. This observation is in agreement with the excited-state *meta* effect.[22−25] For an electron-withdrawing group, its excited-state *meta* effect will decrease the electron density at the *meta* position. Thus, in **12g**, the electron-withdrawing *m*-carbonyl group and the electron-donating *m*-amino group have opposite excited-state *meta* effects, which should hinder heterolysis of the benzylic C—O bond to produce a benzylic cation.

We further infer that in the presence of water, the yield for release of **3** from **11** would be lower because of the possibility of forming **12** in the course of the photoreaction. We postulated that irradiation of **11** in the presence of water would result in the formation of hemiacetal **13** (Scheme 6). There could be competing processes starting from **13**: either photochemical cleavage of the benzylic C—O bond or thermal decomposition of the hemiacetal moiety of **13** to release diol **3** and aldehyde **12**. Meanwhile, photocleavage of a benzylic C—O bond of the acetal moiety of **13** on the other side of the molecule would afford dihemiacetal **14**, which would undergo either photochemical or thermal reaction to release diol **3** along with dialdehyde **15**. Indeed, upon irradiation of **11g** in the presence of water (5:2:2 $CD_3OD/MeCN/D_2O$) under the same conditions, glucoside **3g** was released in 85% yield along with **12g** (8%) and **15** (5%), among other unidentified products, based on ^1H NMR analysis. These results confirm that the presence of water in the photoreaction would decrease the chemical efficiency of release of the diol from **11**.

Scheme 6. Mechanistic Considerations



In summary, two structurally simple PPGs for release of diols have been developed. The 3-dimethylbenzylidene PPG can protect diols in high yields. Both 1,2- and 1,3-diols can be released from the corresponding acetals with high chemical efficiency. Since the working chromophore of the new diol PPG is not changed by photolysis, another benzylidene-type PPG was also developed to protect and release two diols with one PPG molecule.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02777.

> Experimental procedures, full characterization, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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