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Structurally Simple Benzyl-Type Photolabile Protecting Groups for Direct Release of Alcohols and Carboxylic Acids

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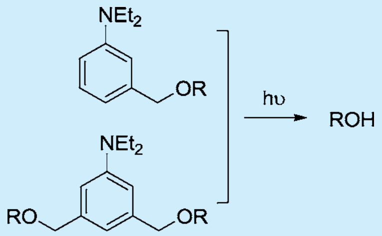
Supporting Information

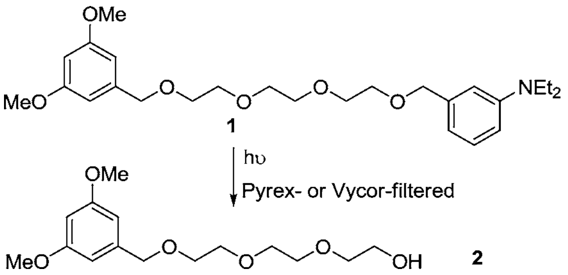
ABSTRACT: Structurally simple benzyl-type photolabile protecting groups (PPGs) have been developed to release alcohols and carboxylic acids. Release of two substrates from one PPG chromophore has also been accomplished.



Efficient photochemical cleavage of covalent bonds is in high demand in many research areas, especially when reactions that take place under neutral and reagent-free conditions with precise spatial and temporal control are desired. One application is for photolabile protecting group (PPG) development.[1−3] PPGs are an indispensable tool in a broad range of basic research and applied sciences.[4−9] Their advantages stem from using light as a traceless reagent in the deprotection process. Despite recent advances in PPG development, ever increasing interest in utilizing a light-controlled approach from a variety of research fields has generated an increasing demand for more new PPGs to complement the existing ones, and "efficient and fast systems for poor leaving groups such as RO$^-$, RHN$^-$ and RS$^-$ are wanted in particular".[1]

In 1962, Barltrop and Schofield first demonstrated that glycine carbamate could be released from benzyl protection upon irradiation at 254 nm.[10] Subsequent efforts toward improving photochemical efficiency of this reaction have been directed to structural variations of the benzyl group by adjusting its aromatic substitution, expansion of the aromatic system, and/or modification at the benzylic carbon.[3] For example, introduction of two methoxy groups at the meta positions of the benzyl group (i.e., 3,5-dimethoxybenzyl (DMBn)) greatly increased the yields of the released amino acids.[11] The term for this substituent effect was coined by Zimmerman as the excited state meta effect.[12−15] However, DMBn only releases a good leaving group such as carbamate or carboxylate but not alkoxide. Recently, Toscano et al. attempted to release diazeniumdiolates from 3-(dimethylamino)benzyl protection;[16] Falvey et al. demonstrated photochemical heterolysis of 3,5-bis(dimethylamino)benzyl ester to release carboxylic acids.[17]

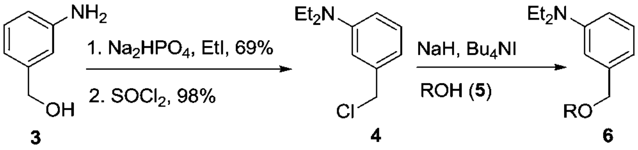
Herein we report our recent discovery that by using only one meta dialkylamino group, the benzylic C−O cleavage was greatly facilitated and poor leaving groups such as alkoxide can be released directly. For example, 15 min irradiation (Vycor, $\lambda > 220$ nm) of **1** (5.0 mM in CD$_3$CN/D$_2$O 9:1),[18] equipped with both DMBn and the new 3-diethylaminobenzyl (DEABn) PPG, only removed the DEABn group in high yield while the DMBn PPG remained intact (eq 1). In a preparative scale reaction of **1** (5.0 mM in methanol), the product **2** was isolated in 93% yield after 90 min irradiation (Pyrex, $\lambda > 280$ nm). We further confirmed the photochemical inertness of DMBn by irradiating DMBn-monoprotected 1,16-hexadecanediol with higher energy UV (i.e., Vycor-filtered) irradiation under the same conditions for 60 min, and only a trace amount of the alcohol was released based on NMR analysis.[19]



(1)

Synthesis of the structurally simple PPG reagent **4**[20] and its installation are straightforward. From commercially available 3-aminobenzyl alcohol **3**, it takes two steps to synthesize the PPG reagent **4** (Scheme 1).[21] Its reaction with an alcohol (**5**) deprotonated by sodium hydride resulted in the corresponding ether **6** in high yields, for example, from primary alcohol 3-

Scheme 1. Preparation of DEABn Ether



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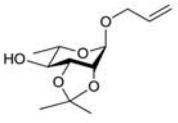
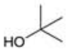
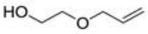
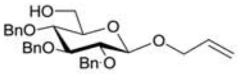
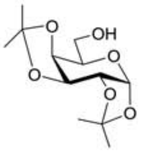
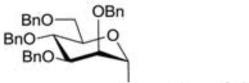
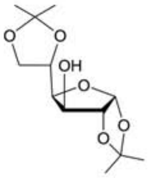
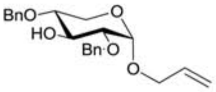
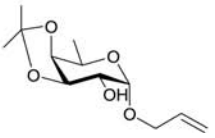
phenyl-1-propanol **5a** to **6a** in 91% yield and from secondary alcohol **5b** to **6b** in 98% yield (Table 1, entries 1 and 2). The ether of tertiary alcohol, i.e., **6c**, was prepared in 91% yield by treating **4** with potassium *tert*-butyloxide (Table 1, entry 3).

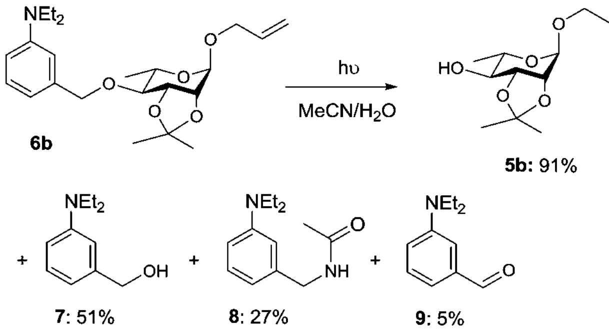
Table 1. Preparation and Photolysis of DEABn Ether

entry	ROH (5)		protection yield (%)	deprotection yield (%)[c]
1		**5a**	91[a]	98
2		**5b**	98[a]	95 (91)
3		**5c**	91[a]	90
4		**5d**	94[b]	94
5		**5e**	94[b]	93 (89)
6		**5f**	89[a]	88 (80)
7	 **5g**		89[b]	88 (86)
8		**5h**	92[b]	81 (81)
9		**5i**	86[b]	91 (87)
10		**5j**	91[b]	88

[a]THF, −10−50 °C. [b]DMF, −10 °C−room temperature. [c]5.0 mM solution (MeCN/water) irradiated with a 450 W medium pressure mercury lamp without deaeration, and yield determined by ^{1}H NMR analysis with isolated yield in parentheses.

Irradiation of DEABn ether **6** (5.0 mM in CD_3CN/D_2O 4:1) with a Pyrex filter for 15 min resulted in release of the primary, secondary, and tertiary alcohols **5a−c** in 98%, 95%, and 90% yield, respectively.[18] The reaction was slightly slower in methanol than in $MeCN/H_2O$. Using deuterated solvent(s) has no apparent effect on the efficiency and cleanness of the reaction.

In a preparative run, irradiation of a 5.0 mM solution of **6b** ($\varepsilon_{308\text{ nm (MeCN)}}$ = 2900 M^{-1} cm^{-1}, Φ = 0.26) in CH_3CN/H_2O (4:1) released the rhamnoside **5b** in 91% isolated yield (eq 2), which confirmed the yield determined by ^{1}H NMR analysis (Table 1, entry 2).



(2)

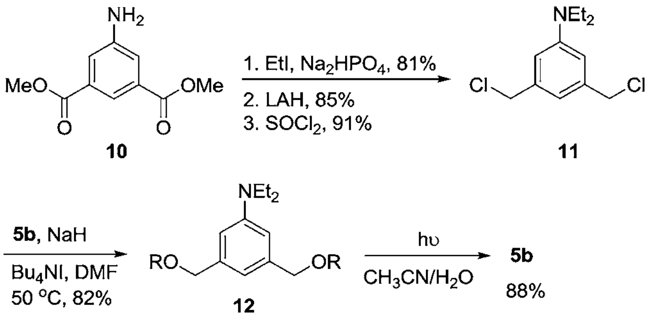
The PPG part was isolated mainly as the benzyl alcohol **7** (51%) and the amide **8** (27%), formed by trapping the benzylic cation intermediate with water and acetonitrile, respectively. The amide **8** (5.0 mM solution in CD_3OD or CH_3OH) is photochemically stable when irradiated (Pyrex filter) for 15 min in control experiments. A minor byproduct **9** was also isolated in 5% yield. Its identity was confirmed by a separate synthesis of **9** from oxidation of **7**. In a control experiment, similar product distributions and reaction efficiencies were obtained in the corresponding deaerated solutions except that the product **9** was not observed.

To further evaluate the DEABn PPG, we examined its protection and deprotection efficiency with a number of alcohols **5d−5j** (Table 1, entries 4−10). High protection and deprotection yields were obtained.

A side-by-side comparison of releasing 3-phenyl-1-propanol from DEABn and DMATr (i.e., 3-(dimethylamino)trityl)[22,23] protection showed similar yields under the same irradiation conditions in both MeCN/water (4:1) and methanol. Comparison of releasing the same alcohol (i.e., 3-phenyl-1-propanol) from DEABn and 2-nitrobenzyl (2-NB)[24,25] protection under the same irradiation conditions revealed complete conversion upon 15 min irradiation in both cases; however, for 2-NB, only 40% of the alcohol was observed after 15 min irradiation in CD_3CN/D_2O (4:1) and 30% in CD_3OD, while DEABn released the alcohol in nearly quantitative yield in both solvent systems. The low efficiency of the 2-NB group likely originates from the slow postirradiation thermal process of substrate release.[26−28] After standing in the dark at room temperature after irradiation, the yield of the released alcohol from 2-NB protection gradually increased to 64% at 4 h and 83% at 25 h in CD_3CN/D_2O, and 42% at 4 h and 77% at 25 h in CD_3OD.

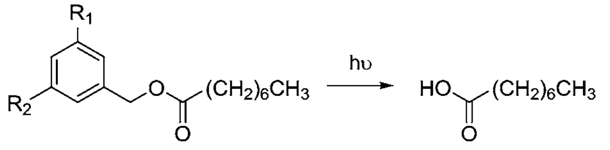
In contrast to the nitrobenzyl series of PPGs, deprotection of DEABn does not destroy the working chromophore. Therefore, we can design a more efficient and structurally simpler PPG which can release two substrates from one chromophore. As shown in Scheme 2, starting from the commercially available dimethyl 5-aminoisophthalate **10**, the PPG reagent diethylaminoisophthalyl chloride (DEAIP-Cl, **11**) was prepared in three steps. Two **5b** alcohol molecules were then protected by one PPG molecule to provide the diether **12** ($\varepsilon_{313\text{ nm (MeCN)}}$ = 3000 $M^{-1}cm^{-1}$). Irradiation of **12** (Pyrex-filtered UV, 5.0 mM) led to complete conversion in 30 min in both CD_3CN/D_2O

Scheme 2. Preparation of DEAIP Ether and Photolysis



(4:1) and CD_3OD.[18] In a preparative run in CH_3CN/H_2O (4:1), the released **5b** was isolated in 88% yield.

DEABn can also protect carboxylic acids. Due to the bathochromic shift of the DEABn's effective absorption (~310 nm) compared with that of DMBn (~279 nm), DEABn and DMBn can be used together for sequential release of carboxylic acids. For example, the ester **13a** (5.0 mM) releases octanoic acid **14** in excellent yield (>97%) in methanol or in MeCN/water (4:1) upon Pyrex-filtered UV irradiation in 1−2 h while the ester **13b** remained intact under the same irradiation conditions.[18] With Vycor-filtered UV irradiation, the conversion of **13a** was 65% in 15 min while the conversion of **13b** was only 23% under the same conditions.[19]



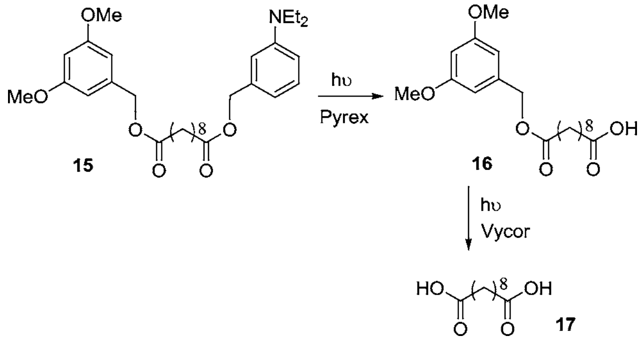
(3)

13a: $R_1 = NEt_2$, $R_2 = H$
13b: $R_1 = R_2 = OMe$

14

We further demonstrated the different photochemical behavior of DEABn and DMBn during irradiation of the diester **15**, equipped with both PPGs (Scheme 3). Thus, irradiation of **15** (5.0 mM in methanol) with Pyrex-filtered UV light completely removed the DEABn and produced the mono ester **16** in 95% yield based on ^1H NMR analysis,[18] in agreement with the 94% isolated yield. Subsequent irradiation of **16** (5.0 mM in CD_3OD) with Vycor-filtered UV light removed the DMBn group to provide the 1,10-decanedicarboxylic acid **17** in 72% yield.[18]

Scheme 3. Sequential Release of Carboxyl Group



It appeared that DEABn released alcohol more efficiently than acid, although carboxylate is a much better leaving group than alkoxide. For example, under the same conditions, 15 min irradiation of **6a−6c** released the alcohols in 90%−98% yield while only 50% of the acid was released from **13a.**[18] This observation is not understood at this time, even though the origin of the excited state meta effect has been investigated.[12−15,17,29−32]

In summary, two new structurally simple benzyl-type PPGs have been developed. The new PPGs are designed on the basis of the excited state meta effect. However, in contrast to the widely known DMBn (also based on the excited state meta effect), the new PPGs release not only acid but also alcohol. Due to the different absorption profiles of DEABn and DMBn, they can be used together for sequential release of carboxylic acids by control of the irradiation wavelength. Moreover, release of two substrates from one chromophore has also been achieved, which should be useful in developing practical photocleavable linkers in various applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, full characterization, and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(18) Irradiation of a 5.0 mM solution in a 5 mm NMR tube with a 450 W medium pressure mercury lamp with an indicated filter sleeve (Vycor, cutoff 220 nm, and Pyrex, cutoff 280 nm) in a Hanovia photoreaction box without deaeration. The yield was determined by ^{1}H NMR spectroscopy analysis unless indicated otherwise.

(19) Reaction was carried out in a quartz cuvette.

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(21) Using a diethylamino group in **2** instead of a dimethylamino group can avoid polymerization of the PPG reagent during PPG installation. However, in terms of photochemical properties, both DEABn and DMABn show similar efficiency in releasing alcohols. In this work, we focus only on the DEABn PPG.

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