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The use of organophotoacids for deprotection reactions in organic synthesis

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Abstract—*o*-Hydroxymethylphenol was found to be an effective and environmentally benign organophotoacid. An increased acidity in the excited state, induced by photoirradiation, was sufficient for the deprotection of several protecting groups which are widely used in organic synthesis.

Certain molecules show interesting properties in their excited states with respect to acidity. Many hydroxyarenes (ArOH) exhibit proton transfer in competition with excited-state decay. Hydroxyarenes have fluorescent conjugate bases with nonbonding oxygen-centered molecular orbitals and excited states with charge distribution at sites distal from oxygen. This reduces the basicity of the excited-state anion, thus increasing the acidity of the conjugate acid.[1] For example, the pK_a value of 2-naphthol in the ground state is 9.5, while that in the excited state is 3.1.[2] Molecules with these properties are called 'super photoacids'. Although a number of synthetic organic reactions using protic (Brønsted) acids have been reported, the use of such organophotoacids in organic synthesis has been investigated only to a minor extent. In this context, we have pursued the aim of utilizing organophotoacids in the development of environmentally benign synthetic organic reactions. In this letter, we report for the first time the effective and environmentally benign use of organophotoacids for the deprotection reactions of several protecting groups which are widely used in organic synthesis (Fig. 1).[3]

In our initial attempts to screen for a suitable organophotoacid for deprotection reactions, we carried out the deprotection reactions of the triethylsilyl (TES) group from substrate **1**, which also possesses a benzyl (Bn) protecting group, using several organophotoacids, such as 2-naphthol (**2**), *o*-, *m*-, *p*-hydroxymethylphenols (**3**–**5**), and *m*-methoxyphenol (**6**), in MeCN, under irradiation from a UV lamp. TES ether is widely used as a protecting group in organic synthesis and is known to be labile under acidic conditions, while Bn ethers are stable under similar conditions.[3] We chose a Blak-ray, 100 W lamp irradiating at 365 nm,[4] because radiation at this long wavelength is not harmful to humans. The strength of the light, which was easily controlled by varying the power level of the lamp and the distance between the lamp and the reaction mixture, was measured using an actinometer.[5] The results of the deprotection reactions carried out under various conditions are summarized in Table 1. It was found that deprotection of the TES group in **1** using organophotoacids **2** and **3** proceeded smoothly to produce alcohol **7** in a good yield (Table 1, entries 1 and 2). Other organophotoacids **4**–**6** did not work well due to their low solubility in the solvent. However, **2** was found to undergo a significant decomposition during the reaction; it was therefore concluded that **3** was superior to **2** as an organophotoacid

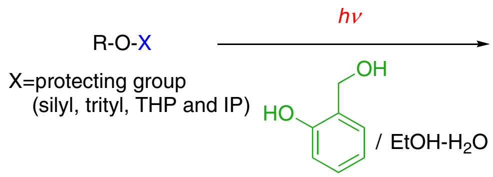

Figure 1. Deprotection reaction using organophotoacid under photoirradiation.

Keywords: Organophotocatalyst; Organophotoacid; Deprotection; Protecting group; Green chemistry.

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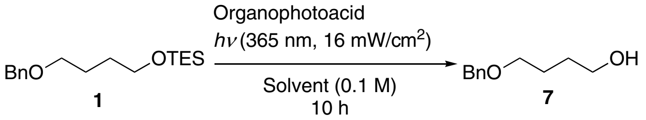
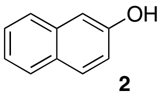
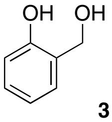
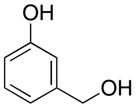
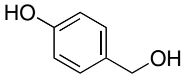
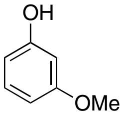
Table 1. Deprotection of TES group in **1** using organophotoacids



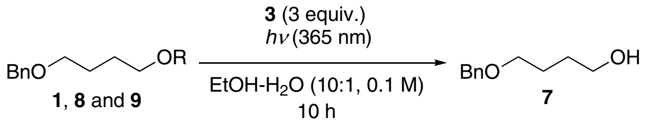
Entry	Organophotoacid	Organophotoacid (equiv)	Solvent	**7**: Yield (%)
1	 **2**	10	MeCN	71
2	 **3**	10	MeCN	70
3	 **4**	10	MeCN	0
4	 **5**	10	MeCN	0
5	 **6**	10	MeCN	0
6	**3**	10	EtOH–H_2O (10:1)	94
7	**3**	5	EtOH–H_2O (10:1)	93
8	**3**	3	EtOH–H_2O (10:1)	95
9	**3**	1	EtOH–H_2O (10:1)	61
10	**3**	0	EtOH–H_2O (10:1)	0

catalyst. Furthermore, a mixture of EtOH and H_2O (10:1) was found to be a more effective solvent than MeCN for the reaction of **1** in the presence of **3**, resulting in a significantly increased yield of **7** (Table 1, entry 6). In this case, it was also confirmed that the silylated derivatives of **3** produced during the reaction were effectively converted into **3** by hydrolysis, with the result that the unchanged **3** was recovered in a >90% yield after the reaction was completed. In addition, it was found that 3 equiv of **3** was a sufficient amount for performing the deprotection reaction satisfactorily with respect to both the chemical yield and the reaction time (Table 1, entry 8).

With these preliminary results in hand, we examined the deprotection reactions of several other silyl groups, such as diethylisopropylsilyl (DEIPS), *t*-butyldimethylsilyl (TBS), triisopropylsilyl (TIPS) and *t*-butyldiphenylsilyl (TPS), as well as the TES group,[3] using organophotoacid **3** under UV irradiation. The results are shown in Table 2. At this stage, we considered the temperature effect due to photoirradiation, and compared the results obtained using the UV lamp with those obtained without UV at the same temperature. It was found that the TES group as well as the DEIPS and TBS groups underwent effective deprotection in the presence of **3** under photoirradiation (Table 2, entries 3 and 5). We confirmed that, in the case of TBS group, deprotection did not occur without photoirradiation, but took place smoothly under photoirradiation (Table 2, entry 5 vs entry 6). Although partial deprotection of the TES and DEIPS groups was observed without photoirradiation (Table 2, entries 2 and 4), it was clear that the efficiency of these reactions was much higher under photoirradiation (Table 2, entry 1 vs entry 2, and entry 3 vs entry 4). These results clearly demonstrate the usefulness of organophotoacid **3** together with photoirradiation in these deprotection reactions. Also, these phenomena indicated that organophotoacid **3** was in the excited state and the acidity significantly increased under photoirradiation as shown in Figure 2. It was confirmed that a stronger light was required for the deprotection of more stable silyl groups, and, in addition, that the most stable silyl groups under acidic conditions, TIPS and TPS, were even less active under the reaction conditions used (data not shown). Therefore, we investigated chemoselective deprotection reactions using several combinations of different silyl groups. As summarized in Scheme 1, it was found that, for the combinations TBS/TES, TIPS/TES, and TPS/TBS, chemoselective deprotection proceeded effectively in the presence of **3** under the appropriate photoirradiation conditions to give the mono-alcohols in good to excellent yields.

Our attention next turned to the reusability of organophotoacid **3**. After the recovery of unchanged **3** in a

Table 2. Deprotection of various silyl groups using **3** under photoirradiation



Entry	R	UV strength (mW/cm^2)	Temperature (°C)	**7**: Yield (%)	**3**: Recovery yield (%)
1	TES: **1**	16	48	95	93
2	TES: **1**	0	48	46	95
3	DEIPS: **8**	27	56	96	93
4	DEIPS: **8**	0	56	11	94
5	TBS: **9**	32	64	95	92
6	TBS: **9**	0	64	0	97

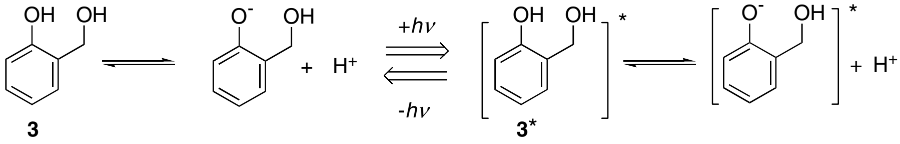
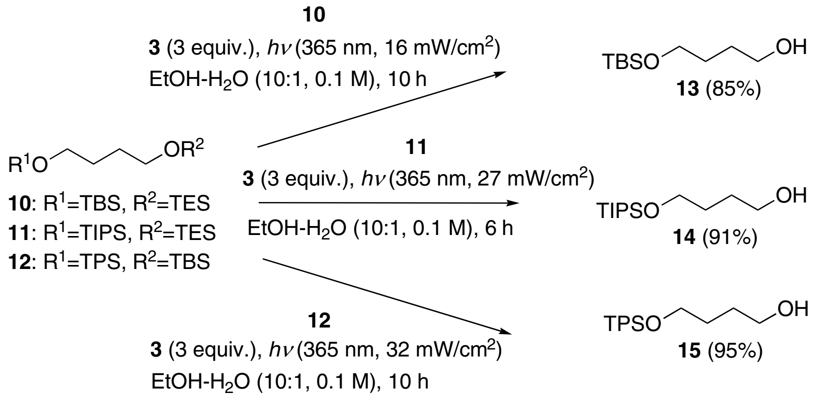


Figure 2. Deprotection reaction profile using **3** under photoirradiation.



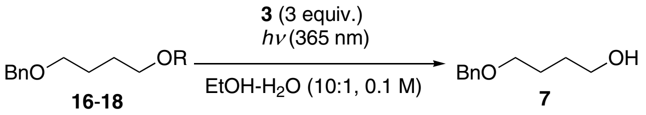
Scheme 1. Chemoselective deprotection of silyl groups using **3** under photoirradiation.

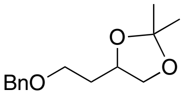
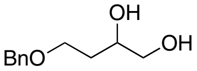
>90% yield (Table 2) via column chromatography concomitant with purification of the product, it was found that the recovered **3** could be reused many times without any loss of efficiency. Furthermore, neither neutralization of the reaction mixture nor extraction of the product was needed after the reaction was completed, because the removal of UV light rendered the reaction mixture almost neutral (the pK_a values of **3** in the ground state and the excited state are 9.9 and 2.9, respectively).[2] The work-up for the reaction involved only evaporation of the solvent, a mixture of EtOH and H_2O, which was also found to be reusable. Overall, the deprotection reaction exhibits several environmentally benign features: (1) non-harmful UV light (365 nm) is used; (2) the solvent (EtOH–H_2O) is non-toxic; (3) catalyst **3** is recoverable and may be reused many times; (4) the work-up involves only evaporation of the solvent, with the result that no waste is produced.

We then applied this novel deprotection method to deprotection reactions of other protecting groups, such as dimethoxytrityl (DMTr), trityl (Tr), tetrahydropyranyl (THP), and isopropylidene (IP) groups, all of which may be removed under acidic conditions.[3] The results are depicted in Table 3. All the deprotection reactions proceeded effectively, to give the corresponding alcohols in good to excellent yields. For the THP and IP groups, a longer reaction time was needed to obtain high yields of the corresponding alcohols (Table 3, entries 5 and 7). Furthermore, the efficiency of the reaction under photoirradiation was again confirmed by comparing the results with those obtained only under heating conditions, without photoirradiation. Moreover, in all cases, organophotoacid **3** was recovered in a >90% yield after completion of the reaction.

The typical experimental protocol for the deprotection of the silyl ether in **1**: To a stirred solution of **1** (0.1 mmol) in EtOH–H_2O (10:1, 0.1 M) was added *o*-hydroxymethylphenol (**3**) (0.3 mmol). After stirring for 10 h under the photoirradiation using a UV lamp (365 nm, 16 mW/cm^2), the mixture was concentrated in vacuo. The purification of the residue by flash column chromatography (silica gel, 8:1 to 1:1 hexane–ethyl

Table 3. Deprotection of various protecting groups using **3** under photoirradiation



Entry	R	UV strength (mW/cm^2)	Temperature (°C)	Time (h)	**7**: Yield (%)	**3**: Recovery yield (%)
1	DMTr: **16**	16	48	10	94	94
2	DMTr: **16**	0	48	10	0	97
3	Tr: **17**	32	64	10	82	96
4	Tr: **17**	0	64	10	29	92
5	THP: **18**	32	64	24	80	93
6	THP: **18**	0	64	24	22	94
7	 **19**	32	64	24	 **20**: 91	95
8	**19**	0	64	24	**20**: 19	94

acetate) gave alcohol **7** in a 95% yield, and **3** was recovered in a 93% yield.[4,5]

In summary, we have developed a novel deprotection method, effective for several protecting groups, using an organophotoacid under photoirradiation. The reaction is highly efficient and environmentally benign. As protection–deprotection reactions are an unavoidable and indispensable step in organic synthesis, this useful method should find wide applications in both academia and industry. The development of several different types of organophotocatalyst, including organophotoacids, and their application in environmentally benign organic synthesis is now under investigation in our laboratories.

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References and notes

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2. Bartok, W.; Hartman, R.; Lucchesi, P. *Photochem. Photobiol.* **1965**, *4*, 499.
3. For reviews of protecting groups, see: (a) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; (b) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994.
4. A Blak-ray (B-100A) purchased from UVP, Inc. was used.
5. A radiometer sensor (UVX-36) purchased from UVP, Inc. was used. UV light at 16 mW/cm^2 was obtained using one lamp placed at 1 cm from the reaction mixture. UV light at 27 and 32 mW/cm^2 was obtained using two lamps placed at 4 cm and 1 cm, respectively, from the reaction mixture.