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Application of the Excited State Meta Effect in Photolabile Protecting Group Design

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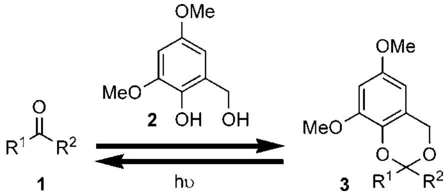
ABSTRACT



A novel photolabile protecting group for carbonyl compounds has been developed, based on the excited state meta effect.

Controllable removal of a photolabile protecting group (PPG) by photochemical means typically requires no chemical reagents and can provide high spatial and temporal resolution. These features are appealing to the researchers in the fields of organic synthesis, solid-phase synthesis, combinatorial chemistry, photolithography, and biochemical and biophysical research.[1] Despite advances in developing PPGs for various applications, practically useful PPGs for some important functional groups (e.g., carbonyl group) are still rare.[2]

Recently, we developed a robust PPG, 2-[hydroxy-(diphenyl)methyl]-4-methoxyphenol, for the protection of carbonyl groups.[3] Herein we report our progress in the development of another novel type of PPG based on the excited state meta effect.[4,5] The meta effect driven PPGs are available for protecting carboxyl groups, amino groups (in the carbamate form), or phosphate esters.[1,4,6] To our delight, we found that the application of the excited-state meta effect could be further expanded.

In our design (Scheme 1), carbonyl compound **1** could be protected by 3,5-dimethoxylsalicylic alcohol (**2**) in a cyclic acetal/ketal form **3**. The $\pi-\pi^*$ excitation of **3** would increase the electron density at C-1 in S_1 owing to the presence of two *m*-methoxyl groups. This charge accumulation at C-1 should facilitate the benzylic C−O breakage, leading to the release of **1**, presumably via the zwitterionic intermediate **4**.

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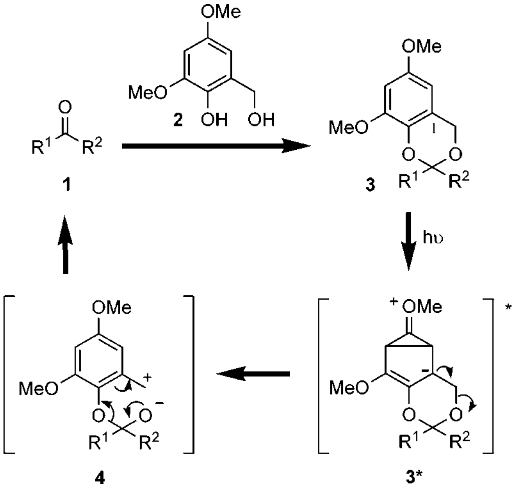
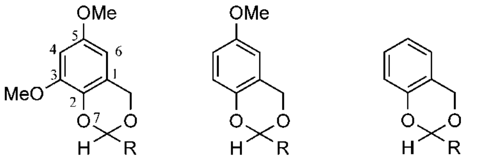
Scheme 1. Protection of Carbonyls with **2**



Excited state computations on the model acetals **5**−**7** revealed that the electron density at C-1 of **5** and **6** increased in S_1 (Figure 1).[7] Model **5** has the largest negative charge accumulation at C-1 in its S_1, which suggests **5** should be more prone to undertake the plausible pathway illustrated in Scheme 1.



5: R = H
3a: R = -$(CH_2)_2Ph$

6: R = H
8: R = -$(CH_2)_2Ph$

7: R = H
9: R = -$(CH_2)_2Ph$

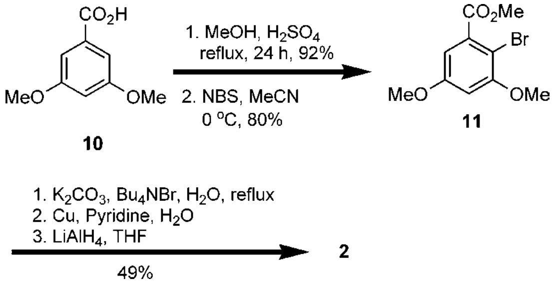
Mulliken Charges:

	5			**6**			**7**		
	C-1	C-2	O-7	C-1	C-2	O-7	C-1	C-2	O-7
S_1	-0.193	+0.410	-0.701	-0.181	+0.433	-0.717	-0.168	+0.429	-0.718
S_0	-0.143	+0.375	-0.724	-0.159	+0.399	-0.742	-0.172	+0.420	-0.744

Figure 1. Comparison of the PPG (**2**) with other models.

To test the computation results, acetals **3a**, **8**, and **9** were thus prepared by reacting 3-phenylpropanal (**1a**) with the corresponding protecting groups under acidic conditions. Salicylic alcohol (for protection in **9**) is commercially available. 5-Methoxylsalicylic alcohol (for protection in **8**) was prepared in one step by reduction of the commercially available 5-methoxylsalicylic acid. 3,5-Dimethoxylsalicylic alcohol **2** was readily synthesized from the commercially available 3,5-dimethoxybenzoic acid (Scheme 2). Thus, esterification of **10** followed by bromination provided **11**.[8]

Scheme 2. Synthesis of the PPG (**2**)



Subsequent saponification, substitution of Br with OH mediated by copper,[9] and reduction with $LiAlH_4$ produced the desired protecting group **2**.

Photochemical reactivity of **3a**, **8**, and **9** correlated well with theoretical computations. Irradiation of **3a** for 1 h led to a **1a**/**3a** ratio of 0.5/1 in CD_3CN/D_2O (9:1),[10] while irradiation of **8** under the same conditions led to a **1a**/**8** ratio of only 0.08/1. For **9**, no observable amount of **1a** was detected. These results suggest that the excited state meta effect should have a significant role in the photochemical deprotection process.

The PPG (**2**) seemed to be promising in protecting carbonyl compounds and was then further examined with other substrates (**1a**−**f**) for its application scope. Carbonyls (**1a**−**f**) were protected with **2** in high yields (Table 1), typically in the presence of a catalytic amount of *p*TsOH and an excess of P_2O_5 in toluene at 0 °C. An alternative protection protocol employed dimethyl ketal of the ketone and the catalyst, $B_{10}H_{14}$ (Table 1, entry 3).[11] The obtained acetals/ketals are reasonably stable and insensitive to the laboratory lighting.[12]

Photochemical releases of carbonyl compounds were best achieved in MeCN with H_2O as the cosolvent without excluding air (Table 1). The obtained 3-phenylpropanal (**1a**) and 2-adamantanone (**1e**) were derivatized and isolated as the corresponding oximes to minimize loss of carbonyls during purifications.[13] Irradiations carried out under nitrogen protection were relatively slower. For example, photoreaction of **3a** under N_2 produced 51% of **1a** with 36% of **3a** recovered after 3 h of irradiation.

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[7] (a) The computations made use of Gaussian 03, Revision C.02, with CIS/3-21G for excited states (nstates = 8) and the geometries were optimized with HF/3-21G.

[8] Bringmann, G.; Hinrichs, J.; Henschel, P.; Kraus, J.; Peters, K.; Peters, E. *Eur. J. Org. Chem.* **2002**, *6*, 1096.

[9] Comdom, P. F. P.; Palacios, M. L. D. *Synth. Commn.* **2002**, *32*, 2055.

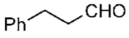
[10] The runs in deuterium solvents were carried out in Pyrex NMR tubes, and the ratios were determined by integrations.

[11] Lee, S. H.; Lee, J. H.; Yoon, C. M. *Tetrahedron Lett.* **2002**, *43*, 2699.

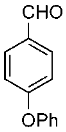
[12] Exploration of the stability of the ketals/acetals was exemplified with **3a**. **3a** was stable under reflux in $MeCN/H_2O$, and was also stable toward the treatment of PhLi at −78 °C, K*t*OBu, $NaBH_4$, or $LiAlH_4$ at room temperature. However, it slowly released **1a** upon treatment with DDQ (20 equiv) at room temperature in MeCN and completely released **1a** after heating with DDQ at 80 °C for 2 h. Treatment with CAN caused decomposition of **3a** with no detection of **1a**. **3a** was stable in the presence of 20 equiv of AcOH (23−80 °C), but it was sensitive to stronger acids such as HCl, TFA, and *p*TsOH. For details, see the Supporting Information.

[13] **3a** and **3e** were stable under the derivatizing conditions. The isolated yields of the oximes are consistent with the yields estimated from ^1H NMR of the underivatized small-scale runs.[10]

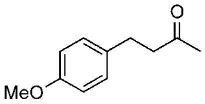
Table 1. Protection and Photorelease of the Carbonyls



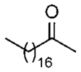
1a



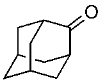
1b



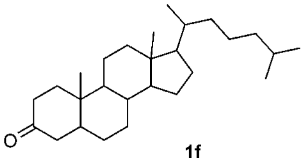
1c



1d



1e

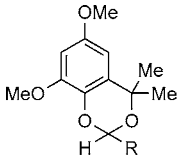


1f

entry	carbonyls	protection yield (%)[a]	deprotection yield (%)[c,d]	recovered s.m. (%)	irradiation time (h)
1	**1a**	92	81[e]	0	4.0
2	**1b**	99	79	6	0.5
3	**1c**	93 (99[b])	86	0	3.0
4	**1d**	91	93[f]	0	3.5
5	**1e**	96	88[e]	6	4.0
6	**1f**	93	86[f]	0	4.0

[a] **2** (0.15 mmol), *p*TsOH (0.002 mmol), carbonyl compound (0.10 mmol), and P_2O_5 (0.2 mmol) in 1.0 mL of toluene, 0 °C, 2−4 h. [b] **2** (0.88 mmol), $B_{10}H_{14}$ (0.028 mmol), and dimethyl ketal of **1c** (0.72 mmol) in 1.5 mL of MeCN, 23 °C, 2.5 h. [c] Irradiated with a 450 W medium-pressure mercury lamp equipped with a Pyrex filter sleeve. [d] Irradiated in 200 mL of MeCN with 50 mL of H_2O. [e] Isolated as the oxime derivatives. [f] Irradiated in 240 mL of MeCN with 10 mL of H_2O.

The PPG (**2**) was not stable under the irradiation conditions and was not detected in any photoreaction mixture.[14] Instead, complex mixtures were obtained in addition to **1** (and **3**) in the photoreactions. We inferred that introduction of benzylic alkyl groups would facilitate the deprotection. It is known that photochemical cleavage of the benzylic C−O bond in the α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl group is more efficient than that in the original PPG without the two benzylic methyl groups.[6] Thus acetal **12** was prepared and photolyzed (Figure 2). Interestingly, contrary to what we expected, irradiation of **12** for 20 min did not show any sign of reaction, while **3a** afforded a **1a**/**3a** ratio of 0.16/1 under the same conditions. However, this observation agreed with the computations,[7] which indicated that the electron density at C-1 of the model molecule **13** increased from −0.066 in S_0 to only −0.118 in S_1, which was less than that in S_1 of models **5**−**7** (Figure 1).



12: R = -$(CH_2)_2$Ph
13: R = H

Figure 2. Structural variation of the PPG (**2**).

In summary, a novel PPG for carbonyl compounds was developed. The PPG was readily installed upon carbonyls in high yields and could be efficiently removed upon UV irradiation. Our experimental results and theoretical computations suggest the photochemical process and the meta effect are correlated.

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Supporting Information Available: Experimental details, spectroscopic data, and NMR spectra for the compounds **2**, **3a**−**f**, **8**, **9**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Photolysis of **2** in CD_3CN/D_2O (4:1) for 2 h caused substantial decomposition of **2**.