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Caging of Carbonyl Compounds as Photolabile (2,5-Dihydroxyphenyl)ethylene Glycol Acetals

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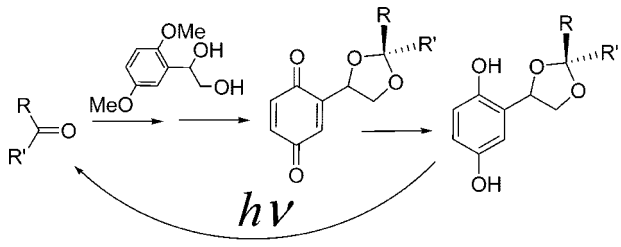

Aldehydes and ketones caged as 4-(2,5-dihydroxyphenyl)-1,3-dioxolanes are efficiently ($\Phi = 0.1-0.2$) released in a good to excellent chemical yield upon irradiation with 300 nm light. Caged carbonyl compounds are prepared by their acetalization with (2,5-dimethoxyphenyl)ethylene glycol followed by oxidative demethylation to produce corresponding (1,3-dioxolane-4-yl)-1,4-benzoquinones. The latter acetals are photochemically inert but can be converted into photolabile hydroquinones by mild reduction in situ.

Photoremovable protecting groups (PPGs) have found numerous applications in organic synthesis, biochemistry, and biotechnology as they allow for the spatial and temporal control of substrate release, while the only reagent required is light.[1,2] The majority of photolabile groups are designed to protect carboxylic acids,[3] phosphates,[4] amines,[5] and alcohols.[6] The choice of PPGs for caging of a carbonyl group, on the other hand, is rather limited. Thus, carbonyl compounds can be released from their dithiane adducts by using PET from suitable internal or external donors.[7] Three types of photolabile acetals also have been reported. 4-(*o*-Nitrophenyl)-[8] and 4,5-bis(*o*-nitrophenyl)-1,3-dioxolanes[9] release carbonyl compounds in a moderate to good yield upon 350 nm irradiation. The byproducts of deprotection, however, contain a nitroso group and are not always compatible with biological applications.[2c,d] The 6-bromo-4-(1,2-dihydroxyethyl)-7-hydroxycoumarin-derived acetals of aldehydes and ketones have good aqueous solubility and can be cleaved under single (365 nm) or two photon (740 nm) excitation conditions albeit in a moderate yield.[10] 5-Methoxy-α,α-diphenylsalicylic alcohol readily forms acetals with aldehydes and ketones under mild conditions and releases substrates in a good yield upon irradiation with $\lambda > 280$ nm.[11] The quantum efficiency of the photochemical cleavage of all these acetals is rather low apparently due to the reversibility of the formation of an intimate ion pair upon light-induced heterolysis of a C−O bond.

We have recently reported a design of PPGs for alcohols and other types of hydroxy groups that utilize the excited state intramolecular proton transfer (ESIPT) in *o*-hydroxybenzyl alcohol analogues.[12] ESIPT-induced C−O bond cleavage produces neutral intermediates and, therefore, proceeds with good quantum efficiency. The PPG for glycols based on this design was also developed.[13] Since deprotection of glycols involves photochemical cleavage of acetals, we decided to explore the applicability of photolabile acetals for the protection of ketones and aldehydes.

Here we report that 300 nm irradiation of (2,5-dihydroxyphenyl)ethylene glycol acetals of aldehydes and ketones **1a**−**e** results in their efficient cleavage and regeneration of the

(1) (a) Greene, T. W.; Wuts, P. G. M. *Greene's Protective Groups in Organic Synthesis*, 4th ed; Wiley: Hoboken, NJ, 2007. (b) Kocienski, P. J. *Protecting Goups*; Thieme: Stuttgart, Germany, 2005.

(2) (a) Pelliccioli, A. P.; Wirz, J. *Photochem. Photobiol. Sci.* **2002**, *1*, 441. (b) Bochet, C. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 125. (c) Morrison, H. *Biological Applications of Photochemical Switches*; Wiley: New York, 1993. (d) Goeldner, M.; Givens, R. *Dynamic Studies in Biology*: Wiley: Weinheim, Germany, 2005. (e) Mayer, G.; Heckel, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4900.

(3) (a) Furuta, T.; Wang, S. S.-H.; Dantzker, J. L.; Dore, T. M.; Bybee, W. J.; Callaway, E. M.; Denk, W.; Tsien, R. Y. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 1193. (b) Sheehan, J. C.; Wilson, R. M.; Oxford, A. W. *J. Am. Chem. Soc.* **1971**, *93*, 7222. (c) Klán, P.; Zabadal, M.; Heger, D. *Org. Lett.* **2000**, *2*, 1569.

(4) (a) Kaplan, J. H.; Forbush, B.; Hoffman, J. F. *Biochemistry* **1978**, *17*, 1929. (b) Walker, J. W.; Reid, G. P.; McGray, J. A.; Trentham, D. R. *J. Am. Chem. Soc.* **1988**, *110*, 7170. (c) Furuta, T.; Torigai, H.; Sugimoto, M.; Iwamura, M. *J. Org. Chem.* **1995**, *60*, 3953. (d) Hagen, V.; Bendig, J.; Frings, S.; Eckardt, T.; Helm, S.; Reuter, D.; Kaupp, U. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1045. (e) Corrie, J. E. T.; Trentham, D. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2409. (f) Givens, R. S.; Athey, P. S.; Kueper, L. W., III; Matuszewski, B.; Xue, J. *J. Am. Chem. Soc.* **1992**, *114*, 8708. (g) Park, C.-H.; Givens, R. S. *J. Am. Chem. Soc.* **1997**, *119*, 2453. (h) Klán, P.; Pelliccioli, A. P.; Pos|Aapil, T.; Wirz, J. *Photochem. Photobiol. Sci.* **2002**, *1*, 920.

(5) (a) Patchornik, A.; Amit, B. J.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 6333. (b) Cameron, J. F.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4303. (c) Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Lu, A. T.; Solas, D. *Science* **1991**, *251*, 767. (d) Chee, M.; Yang, R.; Hubbell, E.; Berno, A.; Huang, X. C.; Stern, D.; Winkler, J.; Lockhart, D. J.; Morris, M. S.; Fodor, S. P. A. *Science* **1996**, *274*, 610. (e) Barltrop, J. A.; Schofield, P. *Tetrahedron Lett.* **1962**, *3*, 697. (f) Chamberlin, J. W. *J. Org. Chem.* **1966**, *31*, 1658. (g) Cameron, J. F.; Wilson, C. G.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1996**, *118*, 12925.

(6) (a) Zehavi, U.; Amit, B.; Patchornik, A. *J. Org. Chem.* **1972**, *37*, 2281. (b) Ohtsuka, E.; Tanaka, T.; Tanaka, S.; Ikehara, M. *J. Am. Chem. Soc.* **1978**, *100*, 4580. (c) Nicolaou, K. C.; Hummel, C. W.; Nakada, M.; Shibayama, K.; Pitsinos, E. N.; Saimoto, H.; Mizuno, Y.; Baldenius, K.-U.; Smith, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 7625. (d) Suzuki, A. S.; Watanabe, T.; Kawamoto, M.; Nishiyama, K.; Yamashita, H.; Ishii, M.; Iwamura, M.; Furuta, T. *Org. Lett.* **2003**, *5*, 4867. (e) Misetic, A.; Boyd, M. K. *Tetrahedron Lett.* **1998**, *39*, 1653. (f) Furuta, T.; Hirayama, Y.; Iwamura, M. *Org. Lett.* **2001**, *3*, 1809. (g) Pirrung, M. C.; Bradley, J.-C. *J. Org. Chem.* **1995**, *60*, 1116.

(7) (a) McHale, W. A.; Kutateladze, A. G. *J. Org. Chem.* **1998**, *63*, 9924. (b) Mitkin, O. D.; Kurchan, A. N.; Wan, Y.; Schiwal, B. F.; Kutateladze, A. G. *Org. Lett.* **2001**, *3*, 1841. (c) Li, Z.; Kutateladze, A. G. *J. Org. Chem.* **2003**, *68*, 8336.

(8) Gravel, D.; Herbert, J.; Thoraval, D. *Can. J. Chem.* **1983**, *61*, 400.

(9) Blanc, A.; Bochet, C. G. *J. Org. Chem.* **2003**, *68*, 1138.

(10) Lu, M.; Fedoryak, O. D.; Moister, B. R.; Dore, T. M. *Org. Lett.* **2003**, *5*, 2119.

(11) Wang, P.; Hu, H.; Wang, Y. *Org. Lett.* **2007**, *9*, 1533.

(12) (a) Kostikov, A. P.; Popik, V. V. *J. Org. Chem.* **2007**, *72*, 9190. (b) Kulikov, A.; Arumugam, S.; Popik, V. V. *J. Org. Chem.* **2008**, *73*, 7611.

(13) Kostikov, A. P.; Popik, V. V. *Org. Lett.* **2008**, *10*, 5277.

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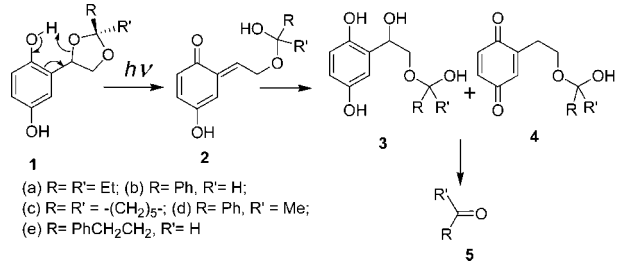
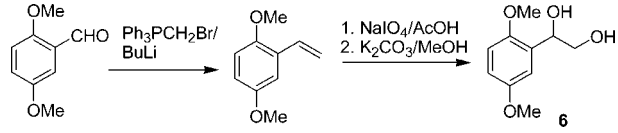
SCHEME 1. Cleavage of Photolablie Acetals



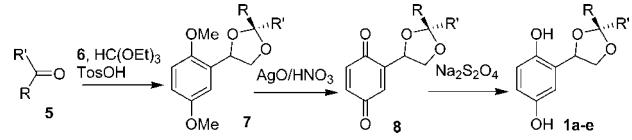
carbonyl compound (Scheme 1). This reaction apparently proceeds via photoinduced transfer of the phenolic proton to the dioxolane oxygen in the 3-position, followed or accompanied by the C−O bond cleavage and the formation of an intermediate *o*-quinone methide **2**. *o*-Quinone methide is very reactive[14] and can undergo rapid hydration or tautomerization to form unstable hemiacetals **3** and/or **4** correspondingly.[12a] The hydrolysis of **3** and **4** liberates the carbonyl compound (Scheme 1). The advantages of this new PPG for carbonyl compounds are in its good aqueous solubility, efficiency of deprotection, and potential for the in situ reductive arming (vide infra).

Preparation of (2,5-dimethoxyphenyl)ethylene glycol **6**, which was required for the synthesis of 4-(2,5-dihydroxyphenyl)-1,3-dioxolanes **1a**−**e**, is outlined in Scheme 2. 2,5-Dimethoxybenzaldehyde was converted into 2,5-dimethoxystyrene[15] under standard Wittig conditions.[16,17] Hydroxylation of the latter with sodium periodate in hot acetic acid, followed by the hydrolysis of the resulting mixture of acetates with potassium carbonate in methanol[18] afforded **6** in 75% yield (Scheme 2).

SCHEME 2. Synthesis of the Glycol 6



SCHEME 3. Synthesis of Acetals 1a−e



Acid-catalyzed acetalization of aldehydes (**5b**,**e**) and ketones (**5a**,**c**,**d**) with glycol **6** in the presence of triethyl orthoformate resulted in the formation of 4-(2,5-dimethoxyphenyl)-1,3-dioxolanes **7a**−**e** (Scheme 3).[17] Oxidative demethylation of the latter with silver oxide/nitric acid[19] produced (1,3-dioxolane-4-yl)-1,4-benzoquinones **8a**−**e** in good yield. It is interesting to note that *p*-benzoquinone-substituted acetals **8a**−**e** are photochemically stable in degassed aqueous methanol solutions. Mild reduction of **8a**−**e** by sodium dithionite in a water−methylene chloride biphasic system afforded the target 4-(2,5-dihydroxyphenyl)-1,3-dioxolanes **1a**−**e** (Scheme 3). The yields of conversion of carbonyl compounds **5a**−**e** into acetals **1a**−**e** are summarized in the Table 1.

TABLE 1. Preparative Yields of Acetals 1a−e and Quantum and Chemical Yields of the Photochemical Release of Carbonyl Compounds at >97% Conversion

acetal	yield of formation, % (over 3 steps)	yield of deprotection, %	Φ_{300}
1a	37	~90[a]	0.08
1b	40	88	0.12
1c	39	59[b]	0.04
1d	47	94	0.15
1e	43	100	0.17

[a] Measured by NMR. [b] Measured by GC.

4-(2,5-Dihydroxyphenyl)-1,3-dioxolanes **1a**−**e** are stable in the dark in the solid state, as well as in aqueous methanol solutions. UV spectra of these compounds contain the characteristic *p*-benzohydroquinone band at 293 nm (log ε = 3.53, Figure 1). Irradiation of solutions of acetals **1a**−**e** in 30% aqueous methanol with 300 nm light results in the efficient release of the carbonyl compound. Figure 1 shows the growth of the characteristic 251 nm band of acetophenone in the course of the photolysis.

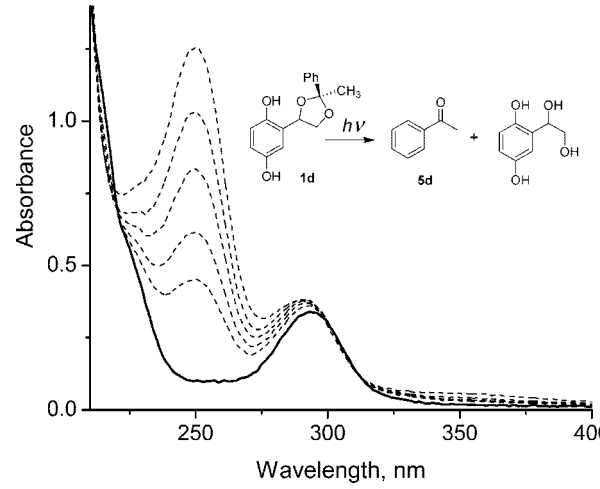


FIGURE 1. UV spectra of **1d** (solid line, ca. 1 × 10^{-4} M in 30% aqueous methanol) and its 300 nm photolysis (dashed lines, every 10 min).

The yields of the substrates release were determined by using either NMR spectroscopy (**5a**), GC (**5c**), or HPLC (**5b**,**d**,**e**); the quantum efficiencies were measured with ferrioxalate chemical actinometry (Table 1).[20]

The quantum yields of the carbonyl compounds release from the photolabile acetals **1a**−**e** is somewhat lower than were observed for other 2,5-dihydroxybenzyl alcohol-based cages.[12a,13] This phenomenon apparently can be explained by the intramolecular nucleophilic attack by the hydroxy group on the intermediate *o*-quinone methide **2**. This reaction results in the ring closure and the regeneration of starting material, and efficiently competes with the hydration of **2** to form hemiacetal **3**.

(14) (a) Diao, L.; Yang, C.; Wan, P. *J. Am. Chem. Soc.* **1995**, *117*, 5369. (b) Wan, P.; Brousmiche, D. W.; Chen, C. Z.; Cole, J.; Lukeman, M.; Xu, M. *Pure Appl. Chem.* **2001**, *73*, 529. (c) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2000**, *122*, 9854. (d) Leo, E. A.; Delgado, J.; Domingo, L. R.; Espinos, A.; Miranda, M. A.; Tormos, R. *J. Org. Chem.* **2003**, *68*, 9643.

(15) Parker, K. A.; Ruder, S. M. *J. Am. Chem. Soc.* **1989**, *111*, 5948.

(16) Wright, J. A.; Gaunt, M. J.; Spencer, J. B. *Chem. Eur. J.* **2006**, *12*, 949.

(17) Experimental details are presented in the Supporting Information.

(18) Emmanuvel, L.; Ali Shaikh, T. M.; Sudalai, A. *Org. Lett.* **2005**, *7*, 5071.

(19) Giles, R. G. F.; Rickards, R. W.; Senanayake, B. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3361.

(20) Murov, S. L.; Carmichael, I.; Hug, G. L. In *Handbook of Photochemistry*; Marcel Dekker: New York, 1993; p 299.

The release of ketone is not accompanied by the bleaching of the 293 nm band. This observation indicates that *p*-benzohydroquinone chromophore is preserved in the course of the reaction and that the hydration of initially formed *o*-quinone methide **2** to the hydroquinone **3** is faster than tautomerization to **4** (Scheme 1). In other words, the reactivity of **2** is drastically different from that of *o*-quinone methide produced in the photolysis of 2,5-dihydroxy benzyl ether and esters.[12a] In the latter case tautomerization to methyl-1,4-benzoquinone was the predominant pathway of the reaction. This reactivity difference is probably due to the inductive effect of the additional oxygen atom in **2**, which increases nucleophilicity of the methide carbon.

In conclusion, a new photolabile acetal was developed for caging of carbonyl compounds. We have shown that ketones and aldehydes can be readily converted into acetals of (2,5-dimethoxyphenyl)ethylene glycol. The *p*-benzoquinone precursor of the 4-(2,5-dihydroxyphenyl)-1,3-dioxolane cage is photochemically inert but can be quantitatively converted in situ into a photoreactive hydroquinone form by using mild reducing agents. The latter acetals efficiently release substrates upon 300 nm irradiation in a good to excellent yield.

Experimental Section

Representative Procedures:[17] **4-(2,5-Dimethoxyphenyl)-2,2-diethyl-1,3-dioxolane (7a).** *p*-Toluenesulfonic acid (ca. 25 mg) was added to a solution of 3-pentanone (**4a**, 950 mg, 11 mmol), (2,5-dimethoxyphenyl)ethylene glycol (6, 2 g, 10 mmol), and triethyl orthoformate (1.8 mL, 1.62 g, 11 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature overnight and then purified by chromatography. A 2.05 g sample of acetal **7a** (7.7 mmol, 77%) was obtained as colorless liquid. ^{1}H NMR δ 0.99 (m, 6H), 1.77 (m, 4H), 3.55 (t, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 4.45 (td, 1H), 5.30 (td, 1H), 6.77 (d, 2H), 7.19 (d, 1H); ^{13}C NMR δ 8.4, 8.5, 29.7, 30.1, 55.9, 56.0, 71.3, 73.6, 111.1, 112.1, 112.9, 113.0, 129.8, 150.7, 154.0; MS 266 (44, M^+), 238 (14), 237 (100), 181 (35), 151 (14), 149 (17), 121 (19), 100 (20), 91 (20), 77 (20); HRMS calcd for $C_{15}H_{22}O_4Na^+$ 289.1416, found 289.1416.

2-(2,2-Diethyl-1,3-dioxolan-4-yl)benzo-1,4-quinone (8a). Silver oxide (1.22 g, 10 mmol) was added to the solution of 4-(2,5-dimethoxyphenyl)-2,2-diethyl-1,3-dioxolane (**7a**, 2.05 g, 7.7 mmol) in dioxane (50 mL) followed by nitric acid (6 M, 1 mL). The resulting suspension was stirred for 30 min and then quenched with sodium bicarbonate (10%, 100 mL). The product was extracted with dichloromethane (3 × 30 mL) and the combined organic phases were washed with $NaHCO_3$ (10%, 2 × 50 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo. Column chromatography of the residue afforded 1.3 g (5.5 mmol, 71%) of **8a** as a yellow oil. ^{1}H NMR δ 0.95 (m, 6H), 1.72 (m, 4H), 3.56 (t, 1H), 4.49 (td, 1H), 4.99 (td, 1H), 6.76 (d, 2H), 6.96 (d, 1H); ^{13}C NMR δ 8.2, 8.4, 29.1, 29.8, 70.2, 72.5, 114.1, 130.7, 136.6, 137.0, 147.6, 187.5, 187.7; MS 207 (26, $[M - 29]^+$), 152 (17), 135 (10), 133 (38), 123 (11), 107 (6), 77 (6), 57 (100); HRMS calcd for $C_{13}H_{16}O_4Na^+$ 259.0946, found 259.0948.

2,2-Diethyl-4-(2,5-dihydroxyphenyl)-1,3-dioxolane (1a). An aqueous solution of sodium dithionite (1.74 g, 10 mmol, 25 mL) was added to a solution of 2-(2,2-diethyl-1,3-dioxolan-4-yl)benzo-1,4-quinone (**7a**, 1.3 g, 5.5 mmol) in dichloromethane (25 mL). The resulting suspension was vigorously stirred for 5 min and the layers were separated. The product was extracted with ether (3 × 30 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. Column chromatography of the residue afforded 875 g of hydroquinone **1a** (3.7 mmol, 67%) as a white solid. ^{1}H NMR (acetone-d_6) δ 0.95 (m, 6H), 1.71 (m, 4H), 3.48 (t, 1H), 4.41 (td, 1H), 5.27 (td, 1H), 6.58 (dd, 1H), 6.67 (d, 1H), 7.01 (d, 1H), 7.81 (s, br, 1H), 7.93 (s, br, 1H); ^{13}C NMR δ 7.86, 7.94, 29.5, 29.9, 71.0, 74.0, 112.5, 112.9, 114.6, 115.8, 127.2, 147.1, 150.7; MS 238 (13, M^+), 209 (11), 152 (90), 135 (62), 123 (42), 107 (32), 95 (6), 77 (13), 57 (100); HRMS calcd for $C_{13}H_{18}O_4Na^+$ 261.1103, found 261.1105.

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Supporting Information Available: Synthesis and characterization of the compounds **1b**−**e**, **6**, **7b**−**e**, and **8b**−**e** and photolyses protocols. This material is available free of charge via the Internet at http://pubs.acs.org.

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