Organic LETTERS

Letter

pubs.acs.org/OrgLett

Caged Fluoride: Photochemistry and Applications of 4-Hydroxyphenacyl Fluoride

Tomáš Slanina,[†] Peter Šebej,[†] Alexander Heckel,[‡] Richard S. Givens,[§] and Petr Klán*[,†]

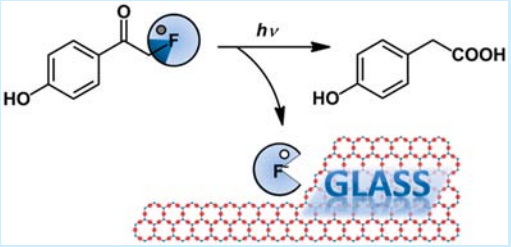
[†]Department of Chemistry and RECETOX, Faculty of Science, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic

[‡]Institute for Organic Chemistry and Chemical Biology, Goethe-University Frankfurt, Max-von-Laue-Str. 9, 60438 Frankfurt, Germany

[§]Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, 5010 Malott Hall, Lawrence, Kansas 66045, United States

Supporting Information

ABSTRACT: The quantitative, efficient (Φ = 0.8) photorelease of the fluoride ion upon UV-irradiation in aqueous media is introduced. The 4-hydroxyphenacyl chromophore is simultaneously transformed into UV-transparent 4-hydroxyphenylacetate via a photo-Favorskii rearrangement. The application of this process is demonstrated by photoinduced etching of mica and silicon by AFM.

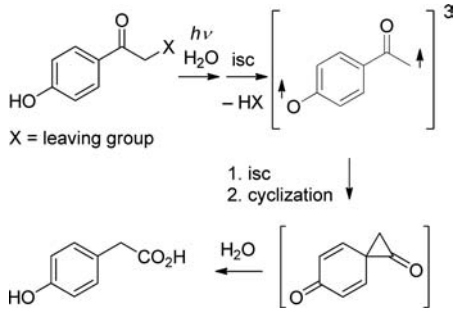


Targeted delivery by release of reactive chemical species with precise spatial and temporal resolution is highly sought after in many technologically driven fields. The fluoride ion, for example, has been recognized as a key effector in the growth and function of mammal hard tissues, such as teeth and bones,[1] cell metabolism,[2] and recently as a key component in fluoride-selective riboswitches in gene regulation.[3] Fluoride is used in dental medicine applications[4] and in organic synthesis, especially for deprotection of silyl protecting groups.[5] Both HF and NH_4F have been widely used for etching of silicon oxide (e.g., glass) and silicon surfaces, especially for microarchitecture fabrication in computer chip production. Normally, a surface is covered with a protective layer or a temporary inhibitor (e.g., photoresist in microchip fabrication)[6a,b] which is subsequently removed by irradiation allowing a chemical agent to modify (etch) the exposed areas.[7a,b] The mechanism of surface etching with fluorides has been thoroughly studied, and fluoride has been found to successfully insert into the Si−H, Si−OH, and Si−Si bonds to form monomeric and small oligomeric molecules of general structure $H_xSi_yF_z$.[8a−c]

The controlled release of reagents from photoremovable protecting groups (PPGs) has been demonstrated to afford exquisite spatial and temporal delivery of biologically active reagents.[9] To our knowledge, only one fluoride-releasing PPG, a 3′,5′-dimethoxydesyl derivative, has been reported,[10] but poor water solubility and a highly absorbing byproduct (causing substantial internal filter effect) have precluded further development.

The 4-hydroxyphenacyl (*p*HP) group photoreleases a wide variety of reagents, possesses excellent water solubility, and efficiently (Φ = 0.1−1.0) and rapidly (k_{obs} = (7−100) × 10^8 s^{-1}) releases the reagent or leaving group. The chromophore is transformed via a photo-Favorskii rearrangement into a phenylacetic acid through rearrangement of the short-lived triplet biradical intermediate (Scheme 1).[11a−d]

Scheme 1. Photochemistry of *p*HP Derivatives



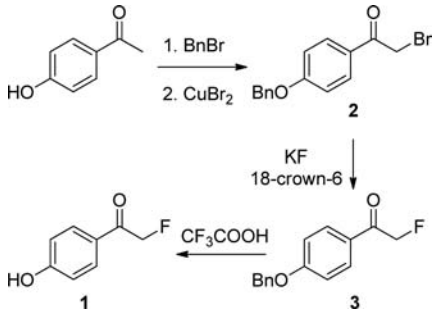
In this work, we introduce 4-hydroxyphenacyl as a photoremovable protecting group for release of the fluoride ion. The chemical yields, quantum efficiencies, and kinetics for F^- release and mechanistic considerations from time-resolved transient absorption measurements are provided along with several surface etching applications.

Synthesis. 4-Hydroxyphenacyl fluoride (**1**) was prepared from 4-hydroxyacetophenone in four steps in 55% chemical yield (Scheme 2). The absorption spectra of **1** in water (pH = 5.0; λ_{max} = 281 nm, ε = 1.12 × 10^4 dm^3 mol^{-1} cm^{-1}; Figure S7) and acetonitrile (λ_{max} = 271 nm, ε = 1.17 × 10^4 dm^3 mol^{-1} cm^{-1}; Figure S7) are similar, and the bands are assigned to the neutral form. In basic aqueous solutions (pH = 10.0), the major absorption band at λ_{max} = 331 nm (ε = 1.74 × 10^4 dm^3 mol^{-1}

Received: August 17, 2015
Published: September 17, 2015

DOI: 10.1021/acs.orglett.5b02374
Org. Lett. 2015, 17, 4814−4817

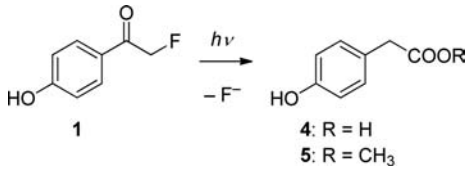
Scheme 2. Synthesis of 4-Hydroxyphenacyl Fluoride (1)



cm^{-1}; Figure S7), similar to that of unsubstituted 4-hydroxyacetophenone,[12] corresponds to the phenolate form of **1**. Only a very weak fluorescence of **1** was observed (Figure S12) in acetonitrile. The pK_a = (7.59 ± 0.06) of the OH group of **1** was determined by spectrophotometric titration using global analysis of the spectra (see Supporting Information for details; Figure S11). Deconvolving the data provided the individual spectra of **1** and its conjugate base, identical to those measured at pH 5 and 10. *p*HP fluoride **1** is chemically stable in aqueous solutions at pH = 5 in the dark for at least 7 days, and less than 10% is consumed in 7 days at pH = 10 (^{1}H NMR).

Photochemistry. Exhaustive irradiation of *p*HP fluoride **1** in aqueous solutions at λ_{irr} = 313 nm led to the release of the fluoride ion, determined by ^{19}F NMR, in very high chemical yields with a disappearance quantum efficiency (Φ_{dis}) of 0.84 ± 0.02 (Scheme 3, Table 1). 4-Hydroxyphenylacetic acid (**4**), which typifies a photo-Favorskii rearrangement,[13a,b] was the exclusive byproduct in aqueous acetonitrile or buffered solutions. Methyl-d_3 ester of 4-hydroxyphenylacetic acid (**5**) was produced along with **4** when **1** was irradiated in CD_3OD solutions. Formation of 4-hydroxybenzyl alcohol, which in some cases[14] accompanies photolysis of *p*HP derivatives, was not observed. *p*HP fluoride was unreactive when photolyzed in acetonitrile (<0.1% water).

Scheme 3. Photoinduced Release of the Fluoride Ion from 1[a]



[a]**5** is formed only in aqueous methanolic solutions.

Table 1. Photochemistry of 1[a]

solvent	yield (F^-)/%	yield (**4**)/%	yield (**5**)/%	Φ_{dis}
acetate buffer[b] pH = 5.0	98	95	n.r.[d]	0.84 ± 0.02[c]
phosphate buffer[b] pH = 10.0	95	95	n.r.[d]	0.051 ± 0.005[c]
CD_3CN/D_2O 1:1 (v/v)	96	93	n.r.[d]	0.75 ± 0.05[e]
CD_3OD/D_2O 1:1 (v/v)	98	59	37	0.84 ± 0.05[e]
CD_3OD/D_2O 3:1 (v/v)	95	39	59	0.79 ± 0.05[e]

[a]Aerated solutions of **1** (c = 10 mmol dm^{-3}) irradiated at (314 ± 2) nm (Figure S27). Each experiment was run at least in duplicate. [b]D_2O-based buffers with 5% of CH_3CN (v/v) as cosolvent (I = 50 mmol dm^{-3}). [c]Solutions ($c \approx 5 \times 10^{-5}$ mol dm^{-3}) irradiated to <15% conversion. Ferrioxalate (Φ = 1.24 in water)[16] was used as an actinometer. All measurements were accomplished at least five times. [d]Not relevant. [e]Solutions ($c \approx 4 \times 10^{-2}$ mol dm^{-3}) in NMR tubes irradiated to ~15% conversion; the concentrations were determined by ^{1}H NMR.

The quantum efficiency of **1** in aqueous buffer at pH = 5.0 was approximately 16-fold higher than that at pH = 10.0, similar to that observed in unbuffered aqueous media (Table 1). This is in accord with a substantially lower reactivity of the 4-hydroxyphenacyl anion compared to that of the neutral form as demonstrated by Givens, Wirz and co-workers before[14] and reflects the energy difference between the neutral triplet of 4-hydroxyacetophenone and its corresponding triplet anion.[11c,15]

Transient Kinetic Study. The transient absorption spectra of **1** (c = 2 mmol dm^{-3}) were recorded in acetate buffer (I = 33 mmol dm^{-3}, 40% aqueous acetonitrile, v/v, pH = 5.0) in 0.15 ps steps up to a 18 ps delay (Figure S13). Immediately after excitation, the transient absorption signal was relatively weak, but its intensity increased at longer delays. Fitting the single exponential kinetics to the data using global analysis[17] gave spectra of two species, which are attributed to the lowest excited singlet (^{1}**1***, λ_{max}(abs) = 315 nm; the deconvolved spectrum is shown in Figure S14) and the triplet excited state (^{3}**1***, λ_{max}(abs) = 405 nm; for the deconvolved spectrum, see Figure S14). The singlet lifetime of ^{1}**1*** was 2.50 ± 0.05 ps (Figure S15) and corresponds to the appearance of the neutral triplet ^{3}**1*** with an intersystem crossing rate constant of k_{isc} = (3.98 ± 0.10) × 10^{11} s^{-1}.[11d]

A strong absorbance of ^{3}**1*** at 405 nm was observed at longer delays after the excitation (>20 ps). The corresponding rate constant for decay of the triplet, $^3k_{decay}$ = (3.20 ± 0.08) × 10^9 s^{-1} (Figures 1 and S17), was assigned to F^- release.

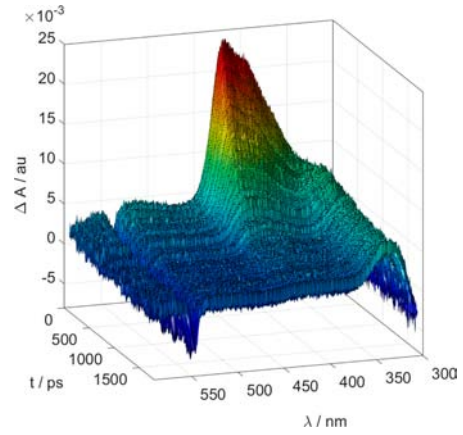


Figure 1. Pump–probe spectra of **1** (c = 2 mmol dm^{-3}) in acetate buffer (pH = 5.0, I = 33 mmol dm^{-3}, with 40% (v/v) of acetonitrile as a cosolvent) reconstructed after global analysis (the time frame <1.7 ns; 10 ps steps).

Concomitant with triplet decay, a weaker signal (λ_{max}(abs) = 330, 420, and 445 nm) arose whose spectrum was obtained from global analysis (Figure S16) and assigned to the 4-oxyphenacyl triplet biradical as a short-lived intermediate[14] previously encountered with other photo-Favorskii rearrangements (Scheme 1). The triplet biradical decays with a rate constant of $k_{dirad} \approx (2.3 \pm 0.2) \times 10^9$ s^{-1} (Figure S17). The

DOI: 10.1021/acs.orglett.5b02374
Org. Lett. 2015, 17, 4814–4817

observed rate constant for F^- release from ^{3}**1*** is similar to other *p*HP decaging rates nicely fitting the correlation of a Brønsted linear free energy relationship for release rate vs pK_a of several other nucleofuge conjugate acids[11d] (Figure S18).

Surface Etching. We performed the following experiments to demonstrate applicability of the fluoride release for surface modifications of silicon-based materials. A freshly prepared surface of mica was covered with a drop of the solution of **1** (c = 22 mmol dm^{-3}) in a 7:3 (v/v) mixture of aqueous acetate buffer (c = 0.1 mol dm^{-3}, pH = 5) and CH_3CN. The samples were either kept in the dark or irradiated using a LED source at λ_{em} = (281 ± 6) nm for 2 h, and subsequently kept in the dark for 14 h. Afterward, the solution was removed, and the surface was inspected by tapping-mode atomic force microscopy (AFM). Nonirradiated surfaces exhibited surface roughness below 300 pm (Figure S21) similar to a fresh mica surface (Figures 2a and S19). The sample exposed to UV light showed

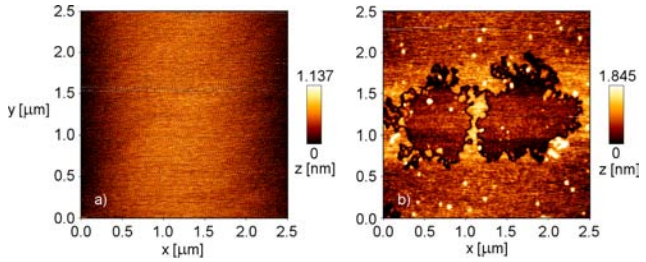


Figure 2. Representative AFM images (2.5 μm × 2.5 μm) of (a) a fresh and untreated mica surface and (b) a mica surface treated with **1** (c = 22 mmol dm^{-3}, in a 7:3 (v/v) mixture of CH_3CN and aqueous acetate buffer (c = 0.1 mol dm^{-3}, pH = 5)) irradiated with LEDs (λ_{em} = 281 ± 6 nm) for 2 h and then left in the dark for 14 h.

distinct flat surface dents of ∼2 nm depth (Figures 2b and S20) suggesting that partial etching of the surface layer(s) occurred. A similar type of etching has been observed upon exposure of the mica surface to HF vapors[18] or HF solutions[19] and has also been suggested as a calibration method for AFM.[20] For this work, the mica surface was also exposed to an aqueous solution of KF (c = 22 mmol dm^{-3}) in the dark, and the resulting changes of the surface (Figure S22) were identical to those found upon irradiation shown in Figure 2b.

In addition, the monocrystalline silicon surface was treated by fluoride released by irradiation of **1** under the same experimental conditions as described above. The silicon surface covered by a solution of **1**, whose original roughness was below 400 pm (Figure S23), remained the same in the dark (Figure S25) but was substantially etched upon UV irradiation. A porous structure evoking small potholes with a height difference up to 1 nm appeared (Figure S24), resembling structural changes observed upon treatment of silicon with aq KF (Scheme S26), aq KOH[21] or upon electrochemical etching using a HF-based electrolyte solution.[22]

Conclusions. 4-Hydroxyphenacyl fluoride (**1**), a caged fluoride, upon exposure to 280−330 nm irradiation efficiently and rapidly releases the fluoride ion while simultaneously converting the phenacyl chromophore into 4-hydroxyphenylacetic acid. A photo-Favorskii mechanism is consistent with the transient absorption experiments. The photorelease of F^- provides a readily available protocol for a temporally and spatially controlled etching of the mica and silicon surfaces by the released fluoride ion from **1**. This protocol has additional potential for application in engineering, material science, and biochemical related applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02374.

Material and methods; Synthetic details; pK_a determination; Irradiation procedures; Time-resolved spectroscopy details; Absorption and emission spectra; NMR spectra; AFM results (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: klan@sci.muni.cz.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support for this work was provided by the Czech Science Foundation (GA13-25775S) (P.K.) and the Deutsche Forschungsgemeinschaft (INST 161/761-1) (A.H.). The RECETOX research infrastructure was supported by the projects of the Czech Ministry of Education (LO1214) and (LM2011028). The authors express their thanks to Dr. Kenneth F. Stensrud (University of Kansas) for performing preliminary experiments. Luboš Jílek is acknowledged for his help with the time-resolved measurements, and Thomas Halbritter (Goethe-University Frankfurt), for his help with AFM. We thank Pavel Friš (Masaryk University) for developing the software for manipulation of the time-resolved data.

■ REFERENCES

(1) Ozsvath, D. *Rev. Environ. Sci. Bio/Technol.* **2009**, *8*, 59−79.
(2) Barbier, O.; Arreola-Mendoza, L.; Del Razo, L. M. *Chem.-Biol. Interact.* **2010**, *188*, 319−333.
(3) Ren, A.; Rajashankar, K. R.; Patel, D. J. *Nature* **2012**, *486*, 85−89.
(4) Wiegand, A.; Buchalla, W.; Attin, T. *Dent. Mater.* **2007**, *23*, 343−362.
(5) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; John Wiley & Sons, Inc.: 2006.
(6) (a) Nakagawa, T.; Tanaka, T.; Niwa, D.; Osaka, T.; Takeyama, H.; Matsunaga, T. *J. Biotechnol.* **2005**, *116*, 105−111. (b) Tsai, Y.-C.; Jen, H.-P.; Lin, K.-W.; Hsieh, Y.-Z. *J. Chromatogr. A* **2006**, *1111*, 267−271.
(7) (a) French, R. H.; Tran, H. V. *Annu. Rev. Mater. Res.* **2009**, *39*, 93−126. (b) Moon, S.-Y.; Kim, J.-M. *J. Photochem. Photobiol. C* **2007**, *8*, 157−173.
(8) (a) Kolasinski, K. W. *Phys. Chem. Chem. Phys.* **2003**, *5*, 1270−1278. (b) Knotter, D. M. *J. Am. Chem. Soc.* **2000**, *122*, 4345−4351. (c) Trucks, G. W.; Raghavachari, K.; Higashi, G. S.; Chabal, Y. J. *Phys. Rev. Lett.* **1990**, *65*, 504−507.
(9) Klán, P.; Šolomek, T.; Bochet, C. G.; Blanc, A.; Givens, R.; Rubina, M.; Popik, V.; Kostikov, A.; Wirz, J. *Chem. Rev.* **2013**, *113*, 119−191.
(10) Boudebous, H.; Košmrlj, B.; Šket, B.; Wirz, J. *J. Phys. Chem. A* **2007**, *111*, 2811−2813.
(11) (a) Givens, R. S.; Jung, A.; Park, C. H.; Weber, J.; Bartlett, W. *J. Am. Chem. Soc.* **1997**, *119*, 8369−8370. (b) Givens, R. S.; Park, C. H. *Tetrahedron Lett.* **1996**, *37*, 6259−6262. (c) Givens, R. S.; Weber, J. F. W.; Conrad, P. G.; Orosz, G.; Donahue, S. L.; Thayer, S. A. *J. Am. Chem. Soc.* **2000**, *122*, 2687−2697. (d) Givens, R. S.; Rubina, M.; Wirz, J. *Photochem. Photobiol. Sci.* **2012**, *11*, 472−488.

DOI: 10.1021/acs.orglett.5b02374
Org. Lett. 2015, 17, 4814−4817

(12) Klíčová, L.; Šebej, P.; Šolomek, T.; Hellrung, B.; Slavíček, P.; Klán, P.; Heger, D.; Wirz, J. *J. Phys. Chem. A* **2012**, *116*, 2935−2944.
(13) (a) Stensrud, K.; Noh, J.; Kandler, K.; Wirz, J.; Heger, D.; Givens, R. S. *J. Org. Chem.* **2009**, *74*, 5219−5227. (b) Sebej, P.; Lim, B. H.; Park, B. S.; Givens, R. S.; Klan, P. *Org. Lett.* **2011**, *13*, 644−647.
(14) Givens, R. S.; Heger, D.; Hellrung, B.; Kamdzhilov, Y.; Mac, M.; Conrad, P. G.; Cope, E.; Lee, J. I.; Mata-Segreda, J. F.; Schowen, R. L.; Wirz, J. *J. Am. Chem. Soc.* **2008**, *130*, 3307−3309.
(15) Conrad, P. G.; Givens, R. S.; Hellrung, B.; Rajesh, C. S.; Ramseier, M.; Wirz, J. *J. Am. Chem. Soc.* **2000**, *122*, 9346−9347.
(16) Hatchard, C. G.; Parker, C. A. P. *Proc. R. Soc. London, Ser. A* **1956**, *235*, 518−536.
(17) Gampp, H.; Maeder, M.; Meyer, C. J.; Zuberbuhler, A. D. *Talanta* **1985**, *32*, 95−101.
(18) Patel, A. R.; Tolansky, S. *Proc. R. Soc. London, Ser. A* **1957**, *243*, 33−40.
(19) Rufe, E.; Hochella, M. F. *Science* **1999**, *285*, 874−876.
(20) Nagahara, L. A.; Hashimoto, K.; Fujishima, A.; Snowden-Ifft, D.; Price, P. B. *J. Vac. Sci. Technol., B: Microelectron. Process. Phenom.* **1994**, *12*, 1694−1697.
(21) Miyake, S.; Wang, M.; Kim, J. *J. Nanotechnol.* **2014**, *2014*, 1−19.
(22) Nayef, U. M.; Muayad, M. W. *Int. J. Basic Appl. Sci.* **2013**, *13*, 15−17.

DOI: 10.1021/acs.orglett.5b02374
Org. Lett. 2015, 17, 4814−4817