ORGANIC LETTERS

2003
Vol. 5, No. 23
4469−4471

# 1-[2-(2-Hydroxyalkyl)phenyl]ethanone: A New Photoremovable Protecting Group for Carboxylic Acids

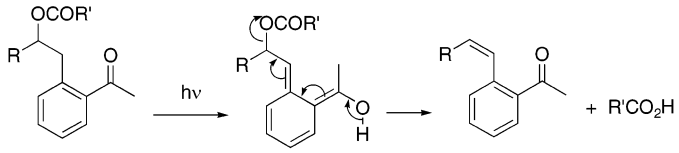
**Walters N. Atemnkeng, Larry D. Louisiana II, Promise K. Yong, Breanne Vottero, and Anamitro Banerjee***

*Department of Chemistry, University of North Dakota, Grand Forks, North Dakota 58202-9024*

*abanerjee@chem.und.edu*

**Received September 15, 2003**

## ABSTRACT




**A new photoremovable protecting group for carboxylic acids is introduced. The protecting group 1-[2-(2-hydroxyalkyl)phenyl]ethanone, HAPE, is used to protect various carboxylic acids. When photolyzed, the protected compound releases the acid in 70–85% isolated yields. The synthesis and the results of photorelease of the protected acids are presented here.**

Photoremovable protecting groups (PRPGs) have been used in a variety of different applications.[1] The temporal and spatial resolution afforded by light along with wavelength control gives PRPGs a distinct advantage over conventional protecting groups in these applications. Despite considerable design and development of PRPGs over the past three decades,[2] the pool of PRPGs is still very small. As a result, there is still considerable interest in developing new PRPGs.[3]

In this paper, a new PRPG for carboxylic acids, 1-[2-(2-hydroxyalkyl)phenyl]ethanone, HAPE (Figure 1), is introduced. The HAPE esters, when photolyzed, are expected to undergo a $\gamma$-H abstraction similar to a Norrish II reaction.

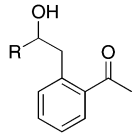



**Figure 1.** 1-[2-(2-Hydroxyalkyl)phenyl]ethanone (HAPE).

This is followed by intersystem crossing to form the enol **1** (Scheme 1). The enol **1** may have two possible configurations: *E* and *Z*.[4] The enol can undergo a keto−enol tautomerism to form the ketone (HAPE ester) or it can eliminate the acid as observed for analogous nitro compounds.[5] Previous reports by Klán et al. indicate that a

(1) (a) Givens, R. S.; Athey, P. S.; Matuszewski, B.; Kueper, L. W., III; Xue, J.-y. *J. Am. Chem. Soc.* **1992**, *114*, 8708−8710. (b) Jayaraman, V.; Hess, G. P. *Biophys. J.* **1998**, *74*, A344-A344. (c) Pirrung, M. C.; Fallon, L.; McGall, G. *J. Org. Chem.* **1998**, *63*, 241−246. (d) Barnhurst, L. A.; Kutateladze, A. G. *Org. Lett.* **2001**, *3*, 2633−2635. (e) Koglin, N.; Lang, M.; Rennert, R.; Beck-Sickinger, A. G. *J. Med. Chem.* **2003**, *46*, 4369−4372. (f) Kessler, M.; Glatthar, R.; Giese, B.; Bochet, C. G. *Org. Lett.* **2003**, *5*, 1179−1181. (g) Vazquez, M. E.; Nitz, M.; Stehn, J.; Yaffe, M. B.; Imperiali, B. *J. Am. Chem. Soc.* **2003**, *125*, 10150−10151.

(2) (a) Pillai, V. N. R. *Organic Photochemistry*; Marcel Dekker: New York, 1987; Vol. 9, pp 225−323. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991; p 473.

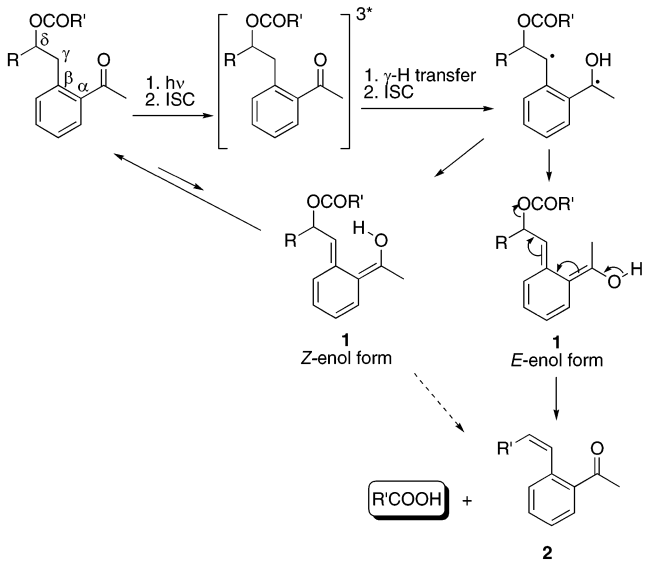
(3) (a) Klán, P.; Zabadal, M.; Heger, D. *Org. Lett.* **2000**, *2*, 1569−1571. (b) Lee, K.; Falvey, D. E. *J. Am. Chem. Soc.* **2000**, *122*, 9361−9366. (c) Bochet, C. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 125−142. (d) Ma, C.; Steinmetz, M. G.; Cheng, Q.; Jayaraman, V. *Org. Lett.* **2003**, *5*, 71−74. (e) Lu, M.; Fedoryak, O. D.; Moister, B. R.; Dore, T. M. *Org. Lett.* **2003**, *5*, 2119−2122.

(4) (a) Chen, C.-P.; Wagner, P. J. *J. Am. Chem. Soc.* **1976**, *98*, 239−241. (b) Haag, R.; Wirz, J.; Wagner, P. J. *Helv. Chim. Acta* **1977**, *60*, 2595−2607.

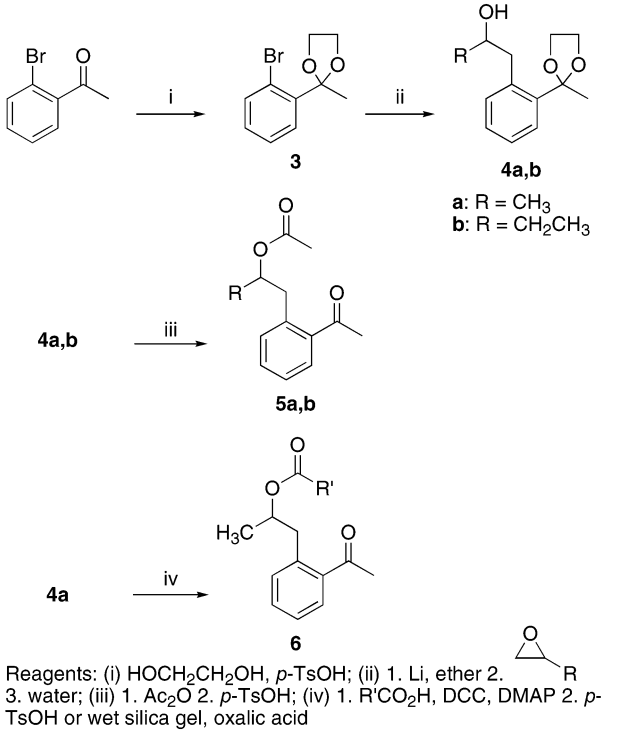
(5) Hasan, A.; Stengele, K. P.; Giegrich, H.; Cornwell, P.; Isham, K. R.; Sachleben, R. A.; Pfleiderer, W.; Foote, R. S. *Tetrahedron* **1997**, *53*, 4247−4264.

10.1021/ol035782q CCC: $25.00 
**Published on Web 10/23/2003**

**Scheme 1.** Proposed Pathway for the Release of Acids from HAPE Esters




**Scheme 2.** Synthesis of HAPE Esters




structurallysimilar *E*-enol of 2′-methylphenacyl esters reketonizes slowly while the *Z*-form undergoes a rapid tautomerization.[6] Although at present we cannot rule out the possibility of the elimination process from the *Z*-form (dashed arrow), it is likely that the elimination of the carboxylic acid occurs only from the *E* form.[7] The elimination leads to the rearomatization of the protecting group. Structurally similar benzophenone derivatives have been shown to release aromatic acids and secondary amines.[8] Recently, Pelliccioli and Wirz have reported the release of HCl from *o*-(2-chloroethyl)acetophenone via a similar photoenol intermediate.[9] A variety of carboxylic acids protected as HAPE esters, when photolyzed released the carboxylic acids in high yields.

This new protecting group offers flexibility to adapt to different application requirements. For example, the **R** group in HAPE (Figure 1) can be chosen as per the requirements of an application without significantly affecting the overall deprotection reaction.

1-[2-(2-Methyl[1,3]dioxolan-2-yl)phenyl]propan-2-ol (**4a**) and 1-[2-(2-methyl-[1,3]dioxolan-2-yl)phenyl]butan-2-ol (**4b**) were synthesized by reacting an organolithium compound with the appropriate epoxide. 2′-Bromoacetophenone was first protected as an ethylene glycol ketal (Scheme 2).[10] The ketal **3** was treated with excess lithium metal in dry diethyl ether and then with the appropriate epoxide. The isolated yields of this reaction varied between 64% (**4a**) and 61% (**4b**). To protect acetic acid, the ketal **4a**,**b** was then refluxed with acetic anhydride for 5 h. The oily product was refluxed with benzene and water mixture for 24 h in the presence of 1 g of *p*-toluenesulfonic acid. The benzene layer was dried, and the solvent was removed to obtain protected acetic acid (yields: 92% for **5a** from **4a** and 86% for **5b** from **4b**). All attempts to remove the ketal from **4a** or **4b** to form HAPE (Figure 1) led to its decomposition. Protected acids **6** were obtained by treating **4a** with the acids in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and catalytic amounts of 4-(dimethylamino)pyridine (DMAP) in $CH_2Cl_2$ [11] (generally 53−86% yield, optimized only for benzoic acid). The ketal was then removed by *p*-toluenesulfonic acid (as described above) or wet silica gel hydrolysis in the presence of oxalic acid (40 °C, 4−5 h, 85−96% yield).[12]

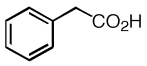
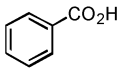
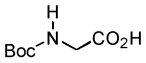
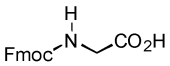
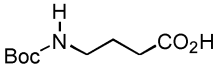
The protected compounds **5a** (4.3 mg in 1.0 mL of $CD_3CN$) and **5b** (4.6 mg in 1.0 mL of $CD_3CN$) were photolyzed in NMR tubes ($\lambda > 320$ nm) under air and under nitrogen. The progress of the reaction was followed by $^1H$ NMR. In a dark control, **5b** (4.3 mg in 1.0 mL of $CD_3CN$) was wrapped in Al foil and placed in front of the light source along with the samples photolyzed. The protected acid **5b** did not decompose in the control experiment. This implies that the protected acids are stable in the dark and can withstand minor temperature fluctuations (that are sometimes experienced during photolysis). The compound **5b** photolyzed under nitrogen decomposed to release acetic acid while no such decomposition occurred when photolyzed under air. This indicates that HAPE releases the carboxylic acid via a

(6) Zabadal, M.; Pelliccioli, A. P.; Klán, P.; Wirz, J. *J. Phys. Chem. A* **2001**, *105*, 10329−10333.
(7) Pelliccioli, A. P.; Klán, P.; Zabadal, M.; Wirz, J. *J. Am. Chem. Soc.* **2001**, *123*, 7931−7932.
(8) Tseng, S.-S.; Ullman, E. F. *J. Am. Chem. Soc.* **1976**, *98*, 541−544.
(9) Pelliccioli, A. P.; Wirz, J. *Photochem. Photobiol. Sci.* **2002**, *1*, 441−458.
(10) Vogel, A. I. *Textbook of Practical Organic Chemistry*, 4th ed.; Longman Group Limited: London, 1978; p 1371.
(11) Grewer, C.; Jäger, J.; Carpenter, B. K.; Hess, G. P. *Biochemistry* **2000**, *39*, 2063−2070.
(12) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63−65.

triplet excited state (Scheme 1). In the presence of oxygen, the triplet excited state is quenched and no acid is released.

A solution of each of the protected acids **6** (ca. 80 mg in 500 mL of $CH_3CN$, $2.5 \times 10^{-4}$ to $6 \times 10^{-4}$ M) was photolyzed with a 450 W mercury lamp using a Pyrex filter for 3−6h. The solvent was removed under reduced pressure, and the residue was dissolved in 20 mL of ethyl acetate or benzene. The solution was then washed with saturated $NaHCO_3$ solution (2 M NaOH solution was used in case of the phenylacetic acid). The organic layer was dried over anhydrous $MgSO_4$ and analyzed for byproducts. The aqueous layer was acidified by dropwise addition of concentrated HCl. The acidified aqueous layer was washed with ethyl acetate or benzene. The organic layer was dried and the solvent was removed under reduced pressure. The recovered acids were analyzed by $^1H$ and $^{13}C$ NMR spectroscopy. The yields, determined gravimetrically, are listed in Table 1. The

**Table 1.** Photolysis Times and Deprotection Yields of the HAPE-Protected Carboxylic Acids

| | acid protected ($R'CO_2H$) | photolysis time (h) | deprotection yield (%) |
|---|---|---|---|
| 1. |  | 6 | 81 |
| 2. |  | 4 | 82 |
| 3. |  | 3 | 73 |
| 4. |  | 4 | 56 |
| 5. |  | 3.5 | 72 |

recovered yield for *N*-fmoc-glycine is lower than others probably due to the instability of the fmoc group in the basic medium during the extraction. This led to only a partial recovery of the released acid.

HAPE-*N*-*t*-BOC-GABA and HAPE-*N*-fmoc-glycine showed no decomposition in $CD_3CN$ when kept in the dark for nearly 4 h (analyzed by $^1H$ NMR and $^{13}C$ NMR). Attempts were made to isolate the free acids from unphotolyzed samples of HAPE-phenylacetate and HAPE-*N*-*t*-BOC-GABA using the base extraction technique described for the photolyzed samples. No detectable free acid could be isolated in the control samples. These experiments rule out the possibility of base-catalyzed hydrolysis of protected acids under the conditions employed for product isolation.

A variety of byproducts were detected in small amounts that were difficult to isolate and characterize. These products formed the bulk of the byproducts. The expected byproduct **2** could not be detected in the mixture although its formation cannot be ruled out. It is possible that **2**, if formed, could act as an internal filter and undergo an efficient secondary photolysis to form oligomers.[13] This along with the competing reketonization could result in low quantum yield for the deprotection reaction as reflected in long photolysis times (3−6 h). The GC−MS analysis of byproducts of the photolysis of **5a** showed a mixture of compounds whose structures could not be conclusively determined.

A variety of different carboxylic acids have been protected by HAPE as esters in relatively high yields. All the HAPE esters released the free acids in high isolated yields under nitrogen. Efforts are currently ongoing to characterize the byproducts of this reaction and to determine the quantum yield of the deprotection reaction. The mechanism of the deprotection reaction is currently under investigation. We hope to trap the enol **1** by Diels−Alder reaction. The results will be reported in the future.

**Acknowledgment.** We thank ND-EPSCoR, the ND-EPSCoR "Network in Catalysis" program (NSF-EPS-0132289), and the University of North Dakota for funding this research. B.V. was supported by NSF REU Grant No. CHE-0243832.

**Supporting Information Available:** Synthesis and NMR spectra of **4ab**, **5ab**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035782Q

(13) (a) DeCosta, D. P.; Bennett, A. K.; Pincock, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 3785−3786. (b) Yu, X.; Scheller, D.; Rademacher, O.; Wolff, T. *J. Org. Chem.* **2003**, *68*, 7386−7399.