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Photosensitized Tetrahydropyran Transfer

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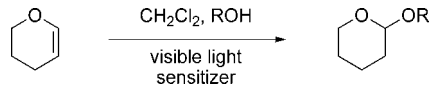

THP ethers were formed cleanly during photolysis of 3,4-dihydro-2*H*-pyran, an alcohol, and catalytic 1,5-dichloro-9,10-anthraquinone with use of visible light. The reaction could be conducted under ambient fluorescent lighting or with sunlight as well as in a Rayonet reactor. The scope and mechanism are discussed.

Photochemistry often provides methods for organic transformations that complement ground state reactions. The utility of photolabile protecting groups is well-documented and further development of such groups is of much current interest.[1] In certain cases, photochemistry can give selectivity based on absorbance, excited state energies, and conformation, potentially reversing selectivities seen in thermal reactions.[2] Additionally, photons are a cheap reagent and generate no waste. The redox and photochemistry of quinones has been studied extensively; this chemistry has been recently applied to photolabile protecting groups in our laboratory and used in synthetic applications elsewhere.[3,4]

Photochemical methods for the protection and deprotection of alcohols are well-known.[5] Methods for similar transformations involving carbonyls and acetals are less widely used. However, photoinitiated release of carbonyl compounds has recently received much attention.[6] Photosensitized conversion of carbonyls to their corresponding dimethyl acetals by photolysis in methanol with various quinones as sensitizer was recently described.[7] This reaction was apparently due to a photochemically generated acid. During the course of our investigation of anthraquinone photochemistry, we have discovered a similar reaction that provides a quick and easy method for installing the tetrahydropyran (THP) protecting group on an alcohol.

We observed that photolysis of a mixture of THP-protected α-terpineol (**1**),[8] 1-pentanol (**2**), and 1,5-dichloro-9,10-anthraquinone (DCQ) in dry dichloromethane using 419 nm Rayonet lamps resulted in transfer of the THP group from **1** to **2**. This proved to be a general reaction: the THP group of **1** was efficiently transferred to other alcohols under the photolysis conditions. The reaction was also observed under standard fluorescent lights or in sunlight. THP transfer was also observed when other THP ethers were photolyzed in the presence of alcohols and DCQ. Apparently, this photolysis produced an equilibrium mixture of the THP ethers. When a 3° THP ether was photolyzed in the presence of either a 2° or 1° alcohol, the THP was completely transferred to the less hindered hydroxyl while photolysis of a 1° THP ether in the presence of a 1° alcohol resulted in a mixture of the possible THP ethers.

The reaction could also be sensitized by *p*-chloroanil (CA). The efficacy of CA was similar to that found by de Lijser in

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SCHEME 1. Photosensitized Formation of THP Ethers

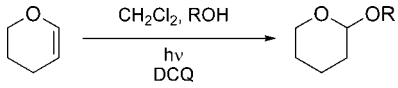


TABLE 1. Photosensitized THP Protection of Alcohols

entry	ROH (THP ether)	solvent (light)[a,b]	yield[c] or (conv)[d]
1	1-C_5H_9OH (**3**)	CH_2Cl_2	99
2	2-C_5H_9OH (**4**)	CH_2Cl_2	91
3	$PhCH_2OH$ (**5**)	CH_2Cl_2	89
4	1-$C_9H_{19}OH$ (**6**)	CH_2Cl_2	96
5	cholesterol (**7**)	CH_2Cl_2	94
6	$CH_3S(CH_2)_3OH$ (**8**)	CH_2Cl_2	90
7	$BOCNH(CH_2)_3OH$ (**9**)	CH_2Cl_2[e,f]	94
8	allyl alcohol (**10**)	CH_2Cl_2	98
9	$CH_2{=}CHC(CH_3)_2OH$ (**11**)	CH_2Cl_2	99
10	$(CH_3)_2C{=}CHCH_2OH$ (**12**)	CH_2Cl_2	86
11	$(CH_3)_2N(CH_2)_2OH$ (**13**)	CH_2Cl_2[g,f]	(0)
12	methyl *p*-hydroxybenzoate (**14**)	CH_2Cl_2	90
13	$TBDMSOCH_2CH_2OH$ (**15**)	CH_2Cl_2	48
14	$PhCH_2OH$ (**5**)	sunlight[h]	98
15	1-C_5H_9OH (**3**)	CH_3CN	(100)
16	α-terpineol (**1**)	CH_3CN[i]	(20)
17	6-methyl-5-hepten-2-ol (**16**)	CH_3CN[i,f]	(0)
18	5-methyl-5-hexen-1-ol (**17**)	CH_3CN[i,f]	(100)
19	$PhCH_2OH$ (**5**)	CH_3CN (Ar)[j]	(62)
20	$PhCH_2OH$ (**5**)	CH_3CN (O_2)[j]	(22)

[a] 30 min irradiation with 8 419 nm lamps in a Rayonet reactor unless otherwise indicated. [b] 5 mol % DCQ unless otherwise indicated. [c] Isolated yield. [d] Conversion measured by GC analysis. [e] 50 min. [f] 50 mol %. [g] 3 h. [h] Sunny day, 1−3 pm local time, late January at 35 °N. [i] 90 min. [j] Reaction mixture purged 20 min with the indicated gas.

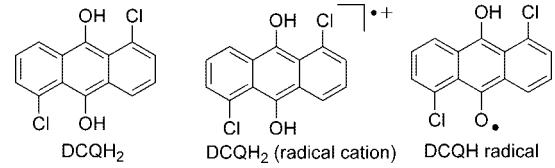
the formation of dimethyl acetals.[7] This similarity led to the hypothesis that a photochemically produced acid was at work in the DCQ-sensitized transfer of THP groups. To test this hypothesis, the reaction was carried out in the presence of base. When solid $NaHCO_3$ was added to the reaction, the rate slowed considerably, but did not completely cease. After 3 h, 90% conversion was achieved. However, in the presence of 5 equiv of 2,6-lutidine, no reaction was observed after 6 h of irradiation.

Installation of a THP group on free hydroxyl groups was also accomplished with use of 3,4-dihydropyran (DHP) (Scheme 1). This proved to be a very clean, efficient method for THP protection of alcohols. Addition of the THP group to 1° alcohols was generally complete in a few minutes, using only 5 mol % DCQ. Results are summarized in Table 1.

Table 1 shows the result of tetrahydropyranylation of alcohols with DHP, DCQ, and visible light. A variety of functional groups were tolerated and even 3° alcohols give good yields. Acid-sensitive groups such as BOC and TBDMS were tolerated. The low yield in the formation of **15** appeared to be a problem in workup and purification. When mono-TBDMS ethylene glycol was mixed with DCQ in CH_2Cl_2 and then photolyzed, no cleavage of the TBDMS group was observed. The addition of water to this photolysis did not change the outcome.

The reaction was relatively insensitive to the presence of oxygen (see below) and was simple to carry out. Typically, DCQ was added to a solution of DHP and alcohol in CH_2Cl_2 and then irradiated. Once the reaction was found to be complete by TLC or GC, the solvent was removed. At that point, the desired THP ether could be isolated either by chromatography or distillation. In many cases, it was possible to dissolve the crude residue in a small amount of cold ether and decant or filter the liquid to separate the THP ether from DCQ. The THP ether thus obtained was better than 95% pure as judged by ^1H NMR.

CHART 1. Possible Photogenerated Acids



Unsatisfactory yields or conversions were observed in three cases. None of the desired THP ether was observed when *N*,*N*-dimethylaminopropanol (entry 11) was used. This was due either to quenching of DCQ by the amine[3a,9] or to the presence of a base, which may neutralize any photogenerated acid. Although both hindered alcohols and potential electron donors were tolerated in some substrates (entries 5, 6, 9, 10, and 12), neither α-terpineol nor 6-methyl-5-hepten-2-ol (entries 16 and 17) gave good yields. In both cases, an alkene located five atoms from the alcohol may allow interaction of acid, alcohol, and alkene. However, 5-methyl-5-hexen-1-ol did give satisfactory conversion (entry 18). The reason for the poor yields in entries 16 and 17 is still under investigation.

An attempt to use DCQ to sensitize the hydrolysis of a THP ether was made by using **5** in 95:5 CH_3CN:H_2O. After 1 h, no reaction had occurred. A few drops of CH_3OH was added and benzyl alcohol was cleanly produced. Although the reaction was slow, complete conversion was achieved. Thus, it appears that THP ethers may either be added or removed with this method. This experiment also demonstrated the importance of including a reducing agent in the reaction mixture.

The data strongly suggest that the photosensitized THP transfer is due to a photochemically generated acid. Addition of base slows or prevents the reaction. Under the reaction conditions, equilibrium is established between the various possible THP ethers and DHP.

Several possibilities exist for the identity of the photogenerated acid. HCl, potentially formed from either DCQ or CH_2Cl_2, was ruled out. In contrast to one report that claimed photolysis of DCQ with visible light resulted in dechlorination to give AQ and HCl,[10] we found that extended photolysis (24 h) of DCQ in CH_3OH/CH_3CN at 419 nm did not result in an increase in acidity and DCQ was obtained unchanged (after reoxidation−photoreduction was evident during the photolysis). Anthraquinone was also capable of sensitizing the reaction. Clean formation of THP ether **5** occurred when AQ was used as sensitizer, although at a slower rate, due to lower absorbance (at 419 nm) by AQ relative to DCQ. Similarly, THP transfer was observed when the reaction was carried out in CH_3CN (entry 13), which ruled out HCl from CH_2Cl_2 as the source of the acid. However, photoreduction of DCQ in CH_2Cl_2 with a small amount of CH_3OH did lead to an increase in acidity.[11] No hydrolysis of the BOC group (entry 7) in the formation of **9** was observed, which also argues against HCl as the acid.

This leaves five possible sources of acid (see Chart 1): $DCQH_2$ (reduced DCQ), $DCQH_2$ radical cation, DCQH radical, $DCQH_2$*, and peroxyl radical (HOO•). All may form during a photoreduction of DCQ.[3a,9] Given our failure to hydrolyze **5** in the absence of a photoreductant, a photoreduction must initiate

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(11) Extraction of the organic solution with neutral water produced an aqueous layer with a pH of approximately 3.

the reaction. The pK_a of $DCQH_2$ is not known, but can reliably be estimated as approximately 10, a value too high to catalyze THP transfer.[12] Likewise, the pK_a of $DCQH_2$* is not known, but true photoacids (that is, compounds that are much more acidic in the excited state) tend to have lifetimes too brief to transfer a proton to anything other than a solvent molecule;[13] in CH_2Cl_2, this seems unlikely, though it cannot be ruled out.

Peroxyl, which can be formed during aerobic photolysis of anthraquinones, has a pK_a of 4.8.[14] The pK_a of the AQH radical is approximately 5.3.[15] Therefore, it is unlikely that the DCQH radical has a pK_a lower than 4. When AcOH (pK_a 4.75) was used to catalyze the reaction (10 mol % AcOH), no conversion was observed after 20 min, while the same reaction sensitized by DCQ (10 mol %) had undergone 80% conversion in the same time. The radical cation of $DCQH_2$ is most likely a much stronger acid than peroxyl and is the conjugate acid of the DCQH radical and was present in approximately the same concentration as these species.[16] Thus, we favored the $DCQH_2$ radical cation as the likely catalytic species.

Unfortunately, distinguishing between the DCQH radical and the $DCQH_2$ radical cation with reaction chemistry was difficult. Both reacted with oxygen and could, therefore, be distinguished from peroxyl. If increasing the O_2 concentration decreased the reaction rate, then peroxyl was not the acid. When carried out under identical conditions, THP transfer in O_2-saturated solution (entry 20) occurred at about one-third the rate as in Ar-saturated solution (entry 19). This result showed that peroxyl was not the acid responsible for THP. Combined with the lack of reaction with AcOH as catalyst, this supports the $DCQH_2$ radical cation as the acid responsible for catalysis in the sensitized reactions. Our investigation of this chemistry continues.

In conclusion, we report a quick and clean photochemical method for introducing a THP group to a hydroxyl group. The method tolerates a variety of functional groups, although strong bases are precluded. The same reaction can also sensitize the hydrolysis of a THP ether. The reaction can be carried out by using photochemical reactors, ambient fluorescent lighting, or sunlight and is only slightly sensitive to the presence of oxygen. This makes the reaction convenient in a typical laboratory setting. The mechanism of the reaction appears to involve a photochemically generated acid that is most likely a reactive anthraquinone intermediate.

(12) Da Silva, R. R.; Ramalho, T. C.; Santos, J. M.; Figueroa-Villar, J. D. *J. Phys. Chem. A* **2006**, *110*, 1031. The pK_a of *p*-hydroquinone is given here as 9.96. The pK_a of 9,10-dihydroxyanthracene is reasonably expected to be similar; the presence of two Cl substituents should lower the pK_a somewhat. This allows a rough estimate of 9 for the pK_a of $DCQH_2$.

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(16) Bordwell, F. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1991**, *113*, 1736. In this paper, the pK_a of the structurally related *p*-hydroquinone radical cation is estimated to be −5.5.

Experimental Section

Representative Procedure for Photochemical THP Ether Formation. 3-Thiomethyl-1-propanol THP Ether (8). To a solution of 3-(methylthio)-1-propanol (128 mg, 1.21 mmol) in dry CH_2Cl_2 was added 3,4-dihydro-2*H*-pyran (111 mg, 1.32 mmol, 1.1 equiv). 1,5-Dichloroanthraquinone (16 mg, 0.06 mmol) was then added to the reaction mixture. The solution was irradiated at 419 nm for 1 h until the 3-(methylthio)-1-propanol was shown to be consumed by GC analysis. The reaction was neutralized with TEA and concentrated in vacuo to afford a yellow oil. The crude product was then dissolved in cold Et_2O and insoluble material removed by gravity filtration. ^{1}H NMR indicated that the crude product thus obtained was quite pure (see the Supporting Information). The oil could be further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate → 6/1 petroleum ether/ethyl acetate) to afford a yellow oil (220 mg, 1.17 mmol, 97%). An analytically pure sample was obtained by vacuum distillation over K_2CO_3 (head temperature of 110 °C (0.5 Torr)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56 (m, 1H), 3.81 (m, 2H), 3.47 (m, 2H), 2.59 (m, 2H), 2.09 (s, 3H), 1.86 (m, 3H), 1.57 (m, 1H), 1.50 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.2, 66.3, 62.7, 31.3, 31.0, 29.7, 25.8, 19.9, 15.8. HRMS (ESI$^+$) calcd for $C_9H_{18}O_2SNa^+$ 213.0919, found 213.0910. Anal. Calcd for $C_9H_{18}O_2S$: C, 56.80; H, 9.53; S, 16.85. Found: C, 56.83; H, 9.53; S, 16.58.

***N-tert*-Butoxycarbonyl-3-amino-1-propanol THP Ether (9).** The crude oil, obtained as described for **7**, could be further purified by flash column chromatography (3/1 petroleum ether/ethyl acetate → 2/1 petroleum ether/ethyl acetate) to yield a yellow oil (200 mg, 0.76 mmol, 94%). An analytically pure sample was obtained by vacuum distillation over K_2CO_3 (head temperature of 130 °C (0.5 Torr)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (s, 1H), 4.57 (m, 1H), 3.62 (m, 2H), 3.47 (m, 2H), 3.24 (m, 2H), 1.71 (m, 4H), 1.55 (m, 4H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 99.0, 78.6, 65.9, 62.0, 39.2, 31.3, 30.4, 28.9, 26.2, 20.0. HRMS (ESI$^+$) calcd for $C_{13}H_{25}NO_4Na^+$ 282.1676, found 282.1666. Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40. Found: C, 60.24; H, 9.77; N, 5.20.

2-(*tert*-Butyldimethylsiloxy)ethanol THP Ether (15). The crude oil, obtained as described for **7**, could be further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate) to give a yellow oil (80 mg, 0.31 mmol, 48%). An analytically pure sample was obtained by vacuum distillation over K_2CO_3 (head temperature of 82 °C (0.5 Torr)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (m, 1H), 3.87 (m, 1H), 3.75 (m, 3H), 3.49 (m, 2H), 1.70 (m, 1H), 1.60 (m 1H), 1.52 (m, 4H), 0.87 (s, 9 H), 0.08 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.9, 68.7, 62.7, 62.0, 30.6, 25.9, 19.4, 18.4, −5.22, −5.25. HRMS (ESI$^+$) calcd for $C_{13}H_{28}O_3SiNa^+$ 283.1699, found 283.1691. Anal. Calcd for $C_{13}H_{28}O_3Si$: C, 59.95; H, 10.84. Found: C, 60.16; H, 10.98.

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Supporting Information Available: Spectroscopic data of compounds **1**, **3**−**9**, **11**, **14**, and **15** and crude products for **3** and **5**, as well as general experimental methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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