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Facile and efficient synthesis of hydroxyalkyl esters from cyclic acetals through aerobic photo-oxidation using anthraquinone-2-carboxylic acid

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ABSTRACT

A convenient metal-free oxidation protocol of various cyclic acetals with molecular oxygen and anthraquinone-2-carboxylic acid under visible light irradiation by a fluorescent lamp afforded their corresponding hydroxyalkyl esters.

1,3-Dioxolanes are among the most widely used protective groups for carbonyl compounds and vicinal diols.[1] Oxidation of 2-aryl- and alkyl-1,3-dioxolanes derived from aldehydes provides a useful route for the synthesis of hydroxyethyl esters, which have been used in selective Diels–Alder reactions, because they can be preferentially activated with Lewis acids by forming a chelated structure in the presence of simple ester groups.[2] Furthermore, hydroxyethyl esters serve as cross-linking agents and fungicides.[3] Metal reagents used for direct oxidative cleavage of 1,3-dioxolanes include molecular oxygen–Co(II),[4] potassium permanganate,[5] and *tert*-butylhydroperoxide in the presence of transition metals.[6] In addition, many methods that employ nonmetal reagents such as ozone,[7] hypochlorous acid,[8] *N*-hydroxyphthalimide in electrochemical oxidation,[9] *tert*-butylhydroperoxide–iodine(III) compounds,[10] IBX/Et_4NBr,[11] (diacetoxy)iodobenzene/LiBr,[12] di-*tert*-butyl peroxide,[13] electrophilic halogen,[14] and *m*-chloroperbenzoic acid in the presence of 2,2′-bipyridinium chlorochromate or boron trifluoride–diethyl ether,[15] sodium perborate in acetic anhydride,[16] and oxone[17] have been reported.

However, there are some problems related to these reactions, such as low yield, hazardous reaction conditions, and the necessity for stoichiometric amounts or environmental high impact catalysts. In contrast, molecular oxygen is thought to be the most desirable oxidant with respect to environmental and economic considerations. Although there have been transition metal-catalyzed oxidative cleavage of cyclic acetals with molecular oxygen as a terminal oxidant,[4] to the best of our knowledge, no metal-free catalytic reactions have been reported, probably because the hydroxy group of hydroxyalkyl esters is easily oxidized in the usual reaction conditions. To develop metal-free catalytic oxidative cleavage of cyclic acetals with molecular oxygen as an oxygen donor, a mild and selective reaction is required.

On the other hand, the effective use of visible light, plentiful in our surroundings, is one of the most important research topics at this time of the hoped-for development of new energy-conversion and energy-using technologies. In our continuous interest in using visible light in organic chemistry, we have been studying photo-oxidative reactions with organo-photocatalysts such as anthraquinones.[18] These reactions proceed under mild reaction conditions such as ambient temperature and pressure, thus it occurred to us that the use of anthraquinones as catalysts makes it possible to perform metal-free catalytic oxidative cleavage of cyclic acetals with molecular oxygen as the terminal oxidant. Herein, we report a facile and efficient oxidative cleavage of cyclic acetals with molecular oxygen as the terminal oxidant under visible light irradiation (Scheme 1).

Table 1 shows the results of the optimization of reaction conditions for the transformation of 2-phenyl-1,3-dioxolane (**1a**),

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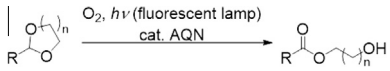
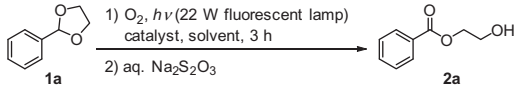


Scheme 1. Oxidative synthesis of hydroxyalkyl esters from cyclic acetals.

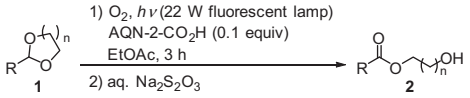
Table 1
Study of reaction conditions



Entry	Catalyst (equiv)	Solvent	Yield[a] (%)
1	Rose Bengal (0.1)	EtOAc	0
2	Methylene blue (0.1)	EtOAc	0
3	1,4-Benzoquinone (0.1)	EtOAc	11
4	2-Cl-AQN (0.1)	EtOAc	57
5	Anthraquinone (AQN) (0.1)	EtOAc	66
6	2-Me-AQN (0.1)	EtOAc	70
7	AQN-2-CO_2H (0.1)	EtOAc	71 (69)
8	AQN-2-CO_2H (0.1)	Acetone	73 (64)
9	AQN-2-CO_2H (0.1)	MeCN	44
10	AQN-2-CO_2H (0.1)	CH_2Cl_2	26
11	AQN-2-CO_2H (0.1)	H_2O	2
12	AQN-2-CO_2H (0.1)	Benzene	0
13	AQN-2-CO_2H (0.1)	*i*-PrOH	0
14	AQN-2-CO_2H (0.05)	EtOAc	70 (64)
15	AQN-2-CO_2H (0.2)	EtOAc	56
16	—	EtOAc	0
17	AQN-2-CO_2H (0.1)	EtOAc	6[b]
18	AQN-2-CO_2H (0.1)	EtOAc	8[c]

[a] ^{1}H NMR yields. Numbers in parentheses are isolated yields.
[b] Under Ar.
[c] In the dark.

Table 2
Oxidative cleavage of cyclic acetals



Entry	1	R	*n*	2	Yield[a] (%)
1	**1b**	4-$MeOC_6H_4$	1	**2b**	77
2	**1c**	4-*t*-BuC_6H_4	1	**2c**	84
3	**1d**	4-MeC_6H_4	1	**2d**	60
4	**1a**	Ph	1	**2a**	69
5	**1e**	4-ClC_6H_4	1	**2e**	73
6	**1f**	4-$CO_2MeC_6H_4$	1	**2f**	67
7	**1g**	4-$NO_2C_6H_4$	1	**2g**	79[b]
8	**1h**	2-$NO_2C_6H_4$	1	**2h**	66[c]
9	**1i**	4-$BocNHC_6H_4$	1	**2i**	15[d]
10	**1j**	4-pyridinyl	1	**2j**	7[c]
11	**1k**	2-thienyl	1	**2k**	24[c]
12	**1l**	*n*-C_5H_{11}	1	**2l**	69
13	**1m**	*n*-$C_{11}H_{23}$	1	**2m**	64
14	**1n**	$PhCH_2$	1	**2n**	45
15	**1o**	4-$MeOC_6H_4$	2	**2o**	61
16	**1p**	4-*t*-BuC_6H_4	2	**2p**	75[e]
17	**1q**	4-MeC_6H_4	2	**2q**	51
18	**1r**	Ph	2	**2r**	65[b]
19	**1s**	4-ClC_6H_4	2	**2s**	49
20	**1t**	4-$NO_2C_6H_4$	2	**2t**	20[f]
21	**1u**	*n*-$C_{11}H_{23}$	2	**2u**	34

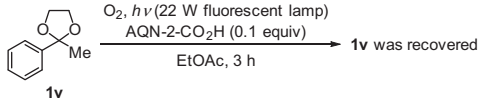
[a] Isolated yields.
[b] 5 h.
[c] 9 h.
[d] 24 h.
[e] With acetone as solvent.
[f] With AQN-2-CO_2H (0.2 equiv) for 9 h.

test substrate, to hydroxyethyl benzoate (**2a**) under a molecular oxygen atmosphere (O_2-balloon) and visible light irradiation at room temperature. Rose Bengal and methylene blue were not effective, in contrast to anthraquinone (AQN) derivatives, and AQN-2-CO_2H was especially suitable for this reaction (entries 1–7). As the result of examination of solvents (entries 8–13), acetone was also a good solvent to afford **2a** in almost the same yield. However, the isolated yield was superior when the reaction was conducted with EtOAc, therefore we decided to use EtOAc as the solvent (entry 7 vs 8). By checking the catalytic amount, 0.1 equiv of AQN-2-CO_2H was found to produce **2a** in the highest yield (entries 7, 14, and 15). Anthraquinone, molecular oxygen, and visible light irradiation are all necessary for this oxidative cleavage because **2a** cannot be satisfactorily obtained without them (entries 16–18).

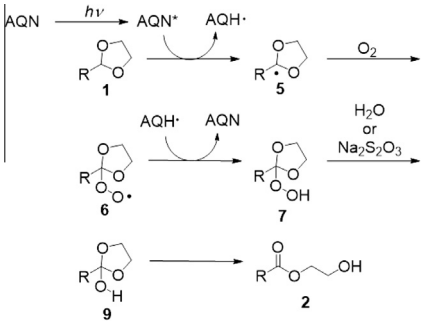
With the optimum reaction conditions in hand, we next investigated the scope and limitations of the oxidative cleavage of 1,3-dioxolanes and 1,3-dioxanes (Table 2).[19] The corresponding hydroxyethyl esters were obtained in good to high yields regardless of electron-donating or electron-withdrawing groups at the *para* position on the aromatic nucleus (entries 1–7). Moreover, **1h**, bearing a nitro group at the *ortho* position, was converted to the desired product in good yields with prolonged reaction time (entry 8). Substrate including NHBoc, pyridinyl, or thienyl was converted to the corresponding hydroxyalkyl ester albeit in low yields (entries 9–11). In addition, aliphatic 1,3-dioxolanes were also converted to hydroxyethyl esters in moderate to good yields (entries 12–14). Although the corresponding hydroxypropyl esters were obtained in good to moderate yields with an electron-donating group at the *para* position on the aromatic nucleus (entries 15–18), an electron-withdrawing group inhibited the reaction, and resulted in low yields (entries 19 and 20). Furthermore, aliphatic 1,3-dioxanes were poor substrates (entry 21). Note that 2-methyl-2-phenyl-1,3-dioxolane (**1v**), an α-disubstituted substrate, was intact under these conditions (Scheme 2). This result suggested that the cleavage of the C–H bond was the initial step of this oxidation.

Scheme 3 shows a plausible path for this reaction, which is postulated by considering the need for irradiation, a catalytic amount of anthraquinone-2-carboxylic acid, and molecular oxygen in this reaction. 1,3-Dioxolane **1** initially reacts with photoexcited anthraquinone-2-carboxylic acid (AQN*) to generate radical species **5**.[18] Compound **5** traps molecular oxygen to afford peroxyradical **6**, which is subsequently transformed to hydroperoxide **7** by the abstraction of a hydrogen atom from **1** or AQH·. Hydroxyalkyl ester **2** is formed from **7** with H_2O or $Na_2S_2O_3$ in the quench step.

In this reaction mechanism, there is a possibility of radical chain process via C–H cleavage of **1** by reacting with radical species **6**. To demonstrate the hypothetical mechanism, we carried out the experiment with intermittent exposure to visible light (Fig. 1). As the result, we observed the conversion of substrate upon to irradiate with fluorescent lamp. In contrast, no transformation was detected in the dark period. This result indicated that the radical chain process did not include and support our estimated mechanism. In addition, excitation of oxygen by photo-excited AQN is probably occurred, but it does not affect this reaction; because both rose Bengal and methylene blue which are known to produce the singlet oxygen were not effective (Table 1, entries 1 and 2).



Scheme 2. Oxidative cleavage of 2-methyl-2-phenyl-1,3-dioxolane.



Scheme 3. Plausible reaction mechanism.

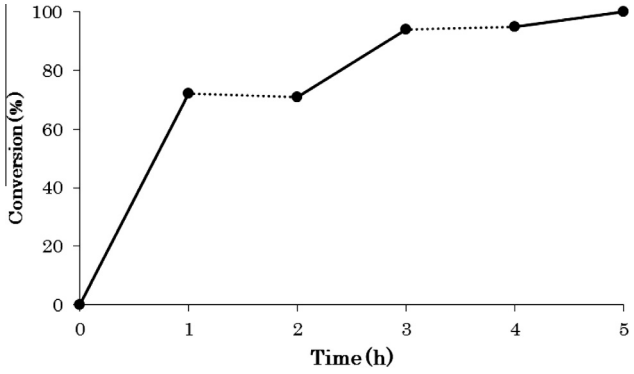


Figure 1. Plot of conversion (%) of 2-phenyl-1,3-dioxolane (**1a**) versus time (h). Solid lines indicate periods of exposure to visible light. Dotted lines indicate periods in the dark.

In conclusion, we have developed a convenient and environmentally benign metal-free oxidative cleavage of various dioxolanes and dioxanes in the presence of molecular oxygen under visible light irradiation from a fluorescent lamp. This new oxidation reaction is appealing to the notion of 'Green Chemistry' because of the nonuse of heavy metals, waste reduction, the use of molecular oxygen, and low cost of reagents. Further application of this oxidation to other reactions is now in progress in our laboratory.

Acknowledgment

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19. A typical procedure (Table 2, entry 4): A dry EtOAc solution (3 mL) of the 2-phenyl-1,3-dioxolane (**1a**, 0.3 mmol), AQN-2-CO_2H (0.03 mmol) in a pyrex test tube equipped with an O_2 balloon, was irradiated for 3 h with four 22 W fluorescent lamps, which were set up at a distance of 65 mm. aq $Na_2S_2O_3$ was added to reaction mixture and extracted with EtOAc, washed with sat. aq NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Pure product was obtained by preparative TLC (*n*-hexane/EtOAc = 5:1) to give ethylene glycol monobenzoate (**2a**) in 69% yield.