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Alternative protocol for oxidation in water: an effective epoxidation system promoted by the combination of Oxone® and an amphiphilic ketone

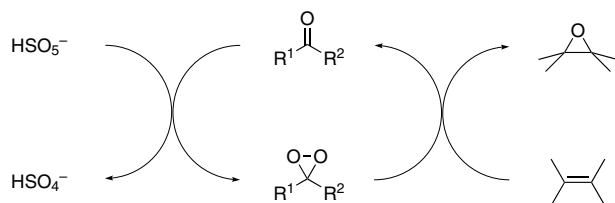Araki Masuyama,* Takashi Yamaguchi, Manabu Abe and Masatomo Nojima

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Abstract—Epoxidation of cyclooctene and other alkenes with Oxone® was promoted effectively in an aqueous micellar solution of an amphiphilic ketone, which was easily derived from hepta(ethylene glycol) monodecyl ether.
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Organic reactions, which can be carried out in water, are highly attractive from the viewpoint of safety and environmental impact.[1] Recently, we proposed a new protocol based on novel amphiphilic hydroperoxides for the oxidation of water-insoluble substrates in aqueous media.[2] We now report that the epoxidation of cyclooctene with Oxone®[†] proceeded effectively in aqueous micellar systems composed of novel amphiphilic ketones **2** and **3**. Oxone® has been applied to a wide variety of organic reactions because it is an inexpensive, easily handled, and water-soluble oxidant.[3] It is well known that the epoxidation of various alkenes by Oxone® is accelerated in the presence of certain ketones as a consequence of in situ dioxirane formation (Scheme 1).[3]

For organic substrates with poor water-solubility, water-miscible organic solvents such as acetonitrile or acetone are often added to aqueous Oxone® solutions. A two-phase system composed of aqueous Oxone® and dichloromethane containing an appropriate phase-transfer catalyst (PTC) is reported to be effective in many cases.[4] The key to our new protocol for the epoxidation of alkenes with Oxone® in water without organic solvent is the formation of an aqueous micellar solution of an amphiphilic ketone that can both solubilize the alkene substrate and promote the Oxone®-mediated epoxidation. In connection with our work, it has been reported that the epoxidation of cinnamic acid derivatives having relatively high water-solubility with Oxone® is promoted in an aqueous $NaHCO_3$ solution of dehydrochloric acid in the absence of both co-solvents and PTC.[5]

The amphiphilic ketones **2** and **3** could be readily prepared by the established methods (Scheme 2).[6‡] The interfacial data[7] for compounds **1**–**3** (Table 1) indicate

**Scheme 1.** Typical reaction mode between ketone and Oxone® in the presence of alkene.

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† Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is the registered trademark in Du Pont. See: http://www.dupont.com/oxone/index.html.

‡ Ketone **2** is a known compound.[6c] *5,8,11,14,17,20,23,26-Octaoxahexatriacontan-2-one* (**3**): isolated by column chromatography on silica gel with an ethyl acetate/ethanol (95:5, v/v) eluent. Yield 60%; an oil; IR (neat, cm^{-1}) 2920, 2850, 1725, 1350, 1250, 1110. ^1H NMR (270 MHz, $CDCl_3$, δ) 0.88 (t, $J = 6.6$ Hz, 3H), 1.27–1.59 (m, 16H), 2.18 (s, 3H), 2.70 (t, $J = 6.4$ Hz, 2H), 3.44 (t, $J = 6.7$ Hz, 2H), 3.61–3.68 (m, 28H), 3.73 (t, $J = 6.4$ Hz, 2H). ^{13}C NMR (67.5 MHz, δ) 14.13, 22.67, 26.08, 29.30, 29.47, 29.54, 29.58, 29.62, 30.44, 31.87, 43.66, 66.07, 70.34, 70.39, 70.49, 70.53, 71.45, 206.87. Anal. Calcd for $C_{28}H_{56}O_9$: C, 62.66; H, 10.52. Found: C, 62.34; H, 10.18.
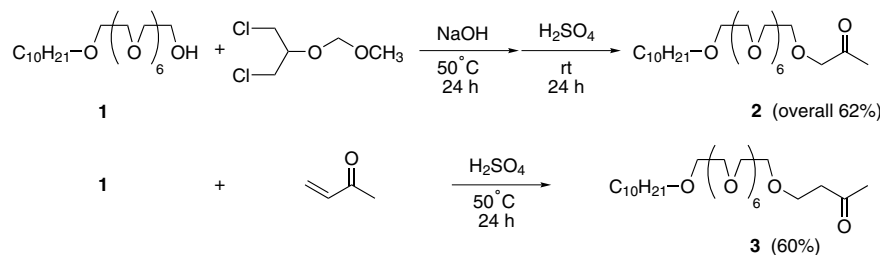
Scheme 2. Preparation of amphiphilic ketones **2** and **3**.

Table 1. Interfacial properties of alcohol ethoxylate **1** and amphiphilic ketones **2** and **3** in water[a]

Amphiphile	T_{cp}/°C	cmc/mM	γ_{cmc}/mN m^{-1}	A[b]/Å^2
1	60	0.90	40	55
2	61	0.68	34	57
3	55	0.62	36	59

[a] The relation between surface tension by the Wilhelmy method and concentration was measured at 20 °C.
[b] Calculated from the plots of surface tension–concentration below each cmc by using the Gibbs adsorption equation within an error of ±5%.
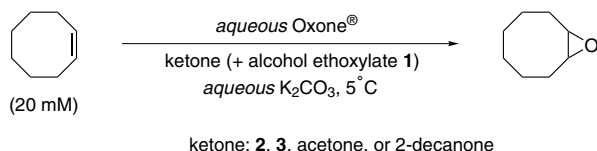
Scheme 3. Epoxidation reaction of cyclooctene by Oxone® in the aqueous micellar solutions.

that neither the terminal acetonyl group nor 3-oxobutyl group make significant changes to the interfacial properties of the parent alcohol ethoxylate **1**.[6,8]

The results of a series of reactions of cyclooctene with Oxone® in water (Scheme 3) are summarized in Table 2.[§]

It was necessary to keep the reaction temperature at 5 °C in this work because both ketones **2** and **3** could completely solubilize cyclooctene below 10 °C under experimental conditions. The epoxidation reaction scarcely proceeded both in the absence of any promoter and in the micellar system composed of **1** only (entries 1 and 2). In contrast to these results, the amphiphilic ketone **2** promoted the epoxidation effectively (entry 3) with epoxycyclooctane being formed quantitatively immediately after the addition of Oxone® was complete. It was noticed in a separate experiment carried out in D$_2$O under the same conditions that ca. 60% of ketone **2** was transformed into the corresponding ester **4** via the Baeyer–Villiger oxidation after the addition of Oxone® as shown in Scheme 4.

Table 2. Epoxidation of cyclooctene with Oxone® at 5 °C in aqueous K$_2$CO$_3$[a]

Entry	Promoter/mM	Oxone®/mM	Time[b]/h	Epoxide[c]/%
1	None	40	0.5	<5
2	**1** (40)	40	0.5	<5
3[d]	**2** (40)	40	0.0	100
4[e]	**3** (40)	40	0.0	53
5[e]	**3** (40)	40	0.5	95
6	**1** (30) + **3** (3)	40	0.5	48
7	**1** (30) + **3** (3)	40	1.0	78
8	**3** (30)	25	0.5	93
9	Acetone (30)	25	0.5	5
10	**1** (30) + Acetone (30)	25	0.5	49
11	2-Decanone (30)	25	0.5	<5
12	**1** (30) + 2-Decanone (30)	25	0.5	5

[a] The reaction was conducted as follows: to a stock solution (3 mL) containing cyclooctene (0.08 mmol), ketone and/or **1**, and K$_2$CO$_3$ (100 mM) was added dropwise an aqueous solution (1 mL) containing Oxone®, K$_2$CO$_3$ (100 mM), and EDTA (0.4 mM) with syringe pump for 0.5 h at 5 °C. In each case, the pH of the stock solution was 10.8 and the pH of the reaction mixture immediately after the addition of Oxone® was 10.0.
[b] From the point of the completion of addition of Oxone®.
[c] The yield of epoxide was determined by the GC analyses as follows: to the reaction mixture was added 1 mL of saturated aqueous sodium thiosulfate followed by 20 mL of saturated aqueous sodium chloride. The mixture was extracted with dichloromethane (3 × 5 mL) and dried over anhydrous MgSO$_4$. The supernatant solution containing a known quantity of internal standard (decane) was injected into the GC apparatus (column, OV-1 capillary).
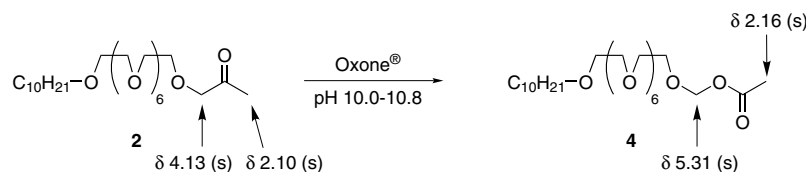[d] About 60% of ketone **2** was converted into the corresponding ester **4** via the Baeyer–Villiger reaction.
[e] The corresponding Baeyer–Villiger ester derived from ketone **3** was not detected under the reaction conditions.

Since Chida et al. found that the ether-bearing α-carbons readily migrated in reference to methyl group in the Baeyer–Villiger reaction,[9] we designed and prepared amphiphilic ketone **3**. The corresponding Baeyer–Villiger ester was not detected after 3 h when the ketone **3** was mixed with Oxone® (3 equiv) in aqueous K$_2$CO$_3$ solution (pH 10.0–10.8) at room temperature. Similarly favorable results were achieved in the epoxidation of cyclooctene by the combination of Oxone® and ketone **3** (entries 4 and 5). Although ketone **3** was not effective as ketone **2** for promoting the Oxone®-mediated epoxidation, the target epoxide was also obtained in excellent yield after 0.5 h of stirring (entry 5).

A catalytic quantity of ketone **3** is also effective (entries 6 and 7) provided that the parent alcohol ethoxylate **1** was

δ 2.16 (s)

$C_{10}H_{21}-O$ ... O ... O ...

2 δ 4.13 (s) δ 2.10 (s)

Oxone®
pH 10.0–10.8

$C_{10}H_{21}-O$ ... O ...

4 δ 5.31 (s)

Scheme 4. Transformation from ketone **2** into the corresponding ester **4** by the Baeyer–Villiger oxidation.

Table 3. Epoxidation of other alkenes (20 mM) with Oxone® in the presence of ketone **3** (30 mM) at 5 °C in water[a]

Entry	Alkene	pH[b]	Oxone®/mM	Time[c]/h	Epoxide[d]/%
1	(Z)-Oct-2-ene	10.0–10.8	30	3.0	83
2	(Z)-Oct-2-ene	7.5–8.0	30	18.0	100
3	(E)-Oct-2-ene	10.0–10.8	30	3.0	29
4	(E)-Oct-2-ene	7.5–8.0	30	18.0	74
5	Styrene	7.5–8.0	40	0.5	97
6	α-Methylstyrene	10.0–10.8	25	1.0	91
7	(E)-β-Methylstyrene	10.0–10.8	40	1.0	88
8	Dec-1-ene	7.5–8.0	40	44.0	43
9[e]	9-Decen-1-ol	7.5–8.0	40	44.0	52
10	Ethyl 3-methylbut-2-enoate	7.5–8.0	40	44.0	81

[a] The reaction was conducted by the similar procedure mentioned in footnote a of Table 2.
[b] In the case of pH 7.5–8.0, a KH_2PO_4 (1 M)–NaOH (1 M) aqueous buffer solution was used.
[c] From the point of the completion of addition of Oxone®.
[d] The yield of epoxide was determined by the GC analyses.
[e] The epoxide was the sole product detected in the reaction mixture.

added to ensure that the micellar system would solubilize the substrate. Also reduction in quantity of Oxone® from 40 mM (2 equiv) to 25 mM (1.25 equiv) did not affect the yield of epoxide under the standard conditions (entry 8).

Acetone and 2-decanone did not promote the epoxidation of cyclooctene with Oxone® in water (entries 9 and 11). In the micellar system composed of alcohol ethoxylate **1**, although 2-decanone was still inactive (entry 12), the combination of acetone and surfactant **1** showed moderate promotional effect on the epoxidation (entry 10). These results suggest that hydrophilic ketones should promote the epoxidation of lipophilic substrates more readily than lipophilic ketones in our micellar system. This is consistent with the properties of the amphiphilic promoters **2** and **3**, which have a carbonyl group at the end of hydrophilic moiety.

This micellar oxidation system is applicable to the epoxidation of other alkenes (Table 3). It should be mentioned first that the pH of the reaction medium plays a crucial role for promotion of the epoxidation with Oxone®. A detailed study on the pH effect is now in progress. (Z)-Oct-2-ene was easier to epoxidize than (E)-oct-2-ene (entries 1–4), which is in accord with the expectations supported by the calculation results.[10] It is noteworthy that less reactive alkenes such as terminal olefin or α,β-unsaturated carbonyl compound can be also converted into the corresponding epoxides in moderate or high yields under neutral conditions with an excess of Oxone® (entries 4, 5, and 8–10). Under the experimental conditions, alkenyl alcohol was selectively oxidized at the C=C bond; other possible products such as the corresponding aldehyde and carb-

oxylic acid were not detected in the reaction mixture (entry 9).

Finally, recovery of ketone **3** from the reaction mixture was attempted on a larger scale reaction. Thus, treatment of cyclooctene (35 mg, 20 mM) with Oxone® (40 mM) in aqueous micellar buffer solution (16 mL) of ketone **3** (259 mg, 30 mM) at 5 °C for 1 h was carried out. After extraction of the mixture with EtOAc (2 × 50 mL), crude products were separated by column chromatography on silica gel. The first fraction (elution with EtOAc) contained epoxycyclooctane (39 mg, 97%). The ketone **3** was isolated from the second fraction (240 mg, 93% recovery; elution with EtOAc/EtOH, 95:5, v/v).

In this preliminary work, we have found that amphiphilic ketone **3** is an effective promoter for the epoxidation of cyclooctene with Oxone® in water under appropriate conditions. Although EtOAc is still required in the separation process, the merit of this micellar system is the epoxidation of alkenes can be carried out in a safe and effective manner in nonflammable and harmless water. Other factors such as the variation of amphiphilic ketones, the pH of the reaction medium, the stirring rate, and the ion strength, which could significantly affect the oxidation reaction with Oxone® in water,[11] are currently under investigation.

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