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Practical and Environmentally Friendly Epoxidation of Olefins Using Oxone

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Abstract:

A practical and efficient epoxidation of aromatic olefins using Oxone in a two-phase system (ethyl acetate−water) is described. The reported method is suitable for large-scale synthesis and does not require phase transfer catalyst (PTC) or pH control.

Introduction

Dioxiranes are highly clean and powerful oxidants and have been applied to a variety of oxidations.[1] Recently Shi and co-workers reported a new method for epoxidation using trifluoroacetone in aqueous acetonitrile as solvent and hydrogen peroxide[2a,b] in place of Oxone (potassium peroxomonosulphate) generally used as dioxiranes generator. Though this method is practical and does not need large amounts of potassium carbonate to neutralize the consequently formed potassium hydrogen sulfate, several problematic features are still evident from the standpoint of large-scale manufactureability. For example, aqueous acetonitrile generally does not readily dissolve aromatic olefins due to their poor solubilities. A more fundamental problem is that toxic and rather expensive acetonitrile is unavoidable as an oxidizing mediator[2b] to ensure high conversion. Recycling of acetonitrile is also difficult mainly due to boiling point which is almost the same as that of water. In the last two decades, two-phase systems have been investigated in order to overcome these problems.[3a−e] These procedures in general used n-Bu4NHSO4 as the phase transfer catalyst (PTC).[3d,4,5] As a result, a tedious dropwise addition of base solution over a long time period under strict pH control was needed to avoid the oxidation of the PTC. From environmental and economical viewpoints, we sought a more practical and efficient procedure using an alternative solvent. Herein we report a practical and environmentally friendly epoxidation procedure using Oxone in a two-phase system (Figure 1).

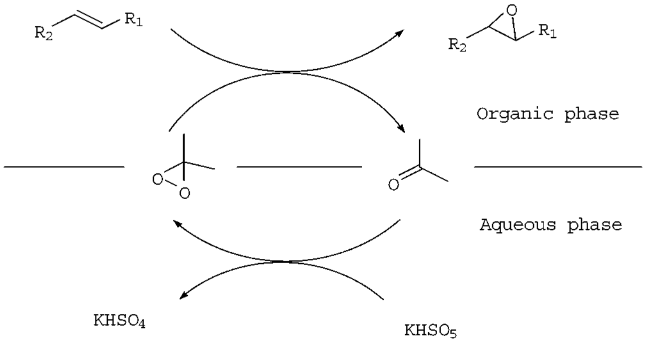

Figure 1. **Biphasic dioxirane epoxidation.**

Table 1. **Concentration of acetone in aqueous phase (20 °C)**

organic solvents	ethyl acetate	dichloro-methane	dichloro-methane & PTC[a]	toluene
distribution[b] in aqueous phase	62%	32%	33%	70%

[a] In the presence of n-Bu$_4$NHSO$_4$ (0.1 equiv). [b] Water, solvent, sodium bicarbonate (5 equiv), and acetone (10 equiv) stirred at room temperature.

Results and Discussion

We selected Oxone as an oxidant since this reagent is stable and commercially available in large quantities. First we evaluated phase transfer catalysts. DMDO (dimethyl dioxirane) is generated in situ from Oxone and a parent ketone, typically acetone. We envisaged that DMDO is more lipophilic than acetone, and thus it might be present in the organic phase even in the absence of a PTC.

As shown in Table 1, the concentration of acetone in the aqueous phase before the addition of Oxone is highest in toluene as the organic solvent. These results indicated that the concentration of DMDO in the aqueous phase would be highest in the two-phase system of toluene−water from a kinetic consideration. On the basis of this study, the improved methodology for the DMDO epoxidation was first applied to the epoxidation of indene. As shown in Table 2 (entry 1), Oxone oxidized the PTC into *n*-Bu4NHSO5 (Trost's salt[6]), easily soluble in organic phase, to cause a background reaction. Further investigation showed the possibility that the reaction might give the expected products in excellent yields even in the absence of PTC (entry 3). We believed that DMDO is present in both of the two phases. Toluene resulted in lower yields against our expectation (entry 7). The affinity of DMDO for the organic solvent is presumably crucial for this reaction. To our surprise, ethyl acetate showed

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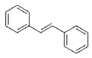
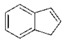
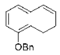
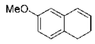
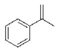
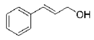
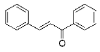
Table 2. **DMDO epoxidation of indene in a two-phase system**

entry	organic solvent	acetone (equiv)	Oxone (equiv)	PTC[a] (equiv)	conversion (%)[b]
1	dichloromethane	0	2.0	0.1	6.4
2	dichloromethane	10	2.0	0.1	99.8
3	dichloromethane	10	2.0	0	90.8
4	ethyl acetate	10	2.0	0	96.4[c]
5	ethyl acetate	10	1.2	0	76.5
6	ethyl acetate	10	1.2[d]	0	80.2
7	toluene	10	2.0	0	78.1[e]

[a] n-Bu_4NHSO_4 added. [b] Calculated by quantitative HPLC analysis. [c] 74.3% of isolated yield. [d] Aqueous Oxone solution added over 2 h. [e] 19.8% of starting material recovered.

Table 3. **Convenient biphasic epoxidation using Oxone (2.0 equiv) and ethyl acetate**

Entry	Olefin	$NaHCO_3$ (equiv)	Conversion (%)[a]	Isolated yields (%)
1a		2.0	47.1	-
1b		5.0	51.7	-
1c[b]		5.0	66.7	65.2
2		5.0	96.4	74.3
3		5.0	96.5	91.8
4		5.0	-	80.9
5		5.0	-	94.3
6		5.0	-	83.1
7		5.0	-	5.3[c]

[a] Calculated by quantitative HPLC analysis. [b] Aqueous Oxone solution added over 2 h. In other entries, Oxone was added over 1 h. [c] Calculated by NMR analysis[9] after purification.

the highest conversion of olefin to epoxide even in the absence of PTC (entry 4).

Dichloromethane is one of the most unfavorable organic solvents for large-scale synthesis from an environmental viewpoint, and exchanging dichloromethane for an alternative solvent is a crucial issue for a pharmaceutical company. As shown in entry 4, the best result was obtained using ethyl acetate as solvent. Thus, this result could expand the applications of DMDO for many kinds of oxidative reactions on a large scale. Efficient conversion of active oxygen is also worth mentioning: 67% of the active oxygen in Oxone was consumed efficiently, owing to the high affinity of DMDO for ethyl acetate, even in the absence of PTC (entry 6). To our knowledge, 32% was the highest recorded conversion in the case of epoxidations using a two-phase system.[3c] The simplicity of this reaction highlights the usefulness of this methodology for large-scale synthesis; addition of excess sodium bicarbonate in the aqueous phase followed by addition of aqueous Oxone solution over a few hours without pH control gave the desired product in excellent yield. Using this methodology, several olefins were successfully converted into epoxides (Table 3). Low reactivity of substrates (entries 1, 7) due to steric hindrance, or electron-withdrawing substituents led to DMDO decomposition to methyl acetate,[8] resulting in a low yield (entry 1a). An important feature of the reaction to ensure high yields is the longer the time taken for the addition of the aqueous Oxone solution, the higher the yield obtained (entry 1c). Other olefins were oxidized in good yields (entries 2−6).

Conclusions

An environmentally friendly and totally practical two-phase epoxidation using Oxone and ethyl acetate was successfully performed without PTC. Further application of this process to other oxidative reactions including an asymmetric epoxidation is under investigation.

Typical Procedure

To a 300-mL three-necked flask were added sodium bicarbonate (3.55 g, 0.0423mol), water (40 mL), acetone (4.90 g, 0.0846mol), ethyl acetate (40 mL), and 1,2-dehydro-5-benzyloxytetralin (2.00 g, 0.00846mol) and were stirred vigorously. An aqueous Oxone solution (Oxone 5.20 g, 0.00846mol, water 36 mL) was added dropwise over 1 h at 20 to 25 °C. The reaction mixture was stirred for an additional 1 h. The organic layer was separated and washed with 20% (w/v) aqueous sodium chloride (20 mL) and then evaporated. The residue was purified by silica gel chromatograpy (silica gel 57 g, n-hexane:ethyl acetate (15:1−10:1), eluant) to give 1,2-dehydro-5-benzyloxytetralin oxide (1.96 g, 0.00777 mol, 91.8% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.15−1.79 (m, 1H), 2.28−2.44 (m, 2H), 3.05−3.13 (m, 1H), 3.73 (m, 1H), 3.84 (d, 1H, $J = 4.2$), 5.06 (s, 2H), 6.92 (d, 1H, $J = 8.0$), 7.03−7.41 (m, 7H). Mass (TIC, m/z): 253 (M + 1). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.18; H, 6.25

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