

Hydroperoxidation of 9-Hexylfluorene and Weitz-Scheffer Epoxidation of Cyclohexenones under Phase Transfer Condition

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A single-pot oxidation system involving hydroperoxidation of 9-hexylfluorene and epoxidation of cyclohexenones therewith under phase transfer condition was devised and applied tentatively to asymmetric synthesis of optically active epoxyketones.

KEY WORDS: Phase transfer catalyst/ Hydroperoxidation/ Single-pot epoxidation/ Asymmetric Epoxidation/

INTRODUCTION

Utilization of molecular oxygen to epoxide synthesis without involving any isolation procedure of hazardous hydroperoxides as epoxidizing agent has been an important problem standing on the safety and effective use of natural resources. A number of studies in this field have been reported including metal catalyzed hydroperoxidation and epoxide formation *in situ*,¹⁾ photochemical method,²⁾ P-450 model system³⁾ and phase transfer-catalyzed oxidations⁴⁾ in all of which molecular oxygen was used as one oxygen atom source.

We report here a single-pot epoxidation of cyclohexenones in which both 9-hexylfluorenyl hydroperoxide formation via anion oxidation with molecular oxygen and the epoxidation are conducted successively under phase transfer condition. In due course, the system was tentatively extended to the asymmetric synthesis of optically active epoxyketones by use of chiral phase transfer catalyst (PTC).

RESULT AND DISCUSSION

Our previous work showed that 9-hydroperoxy-9-hexylfluorene(1) was a good candidate for the Weitz-Scheffer type epoxidation (eq. 1) improving the enantioselectivity of asymmetric epoxidation of cyclohexenone by use of an optically active bis-type phase transfer catalyst.⁵⁾ This hydroperoxide (1) was prepared previously by Sprinzak from 9-hexylfluorene and dry oxygen gas in the presence of triton B

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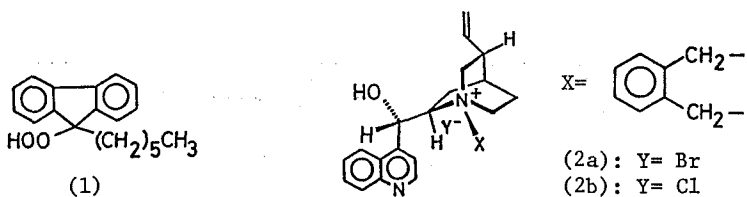
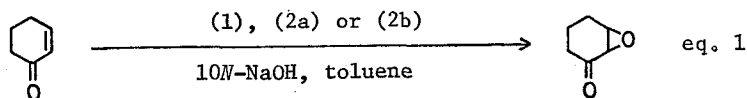


Fig. 1.

in dry pyridine (eq.2).⁶⁾ In order to find more convenient reaction conditions, we examined the fluorenyl anion-mediated hydroperoxidation by use of benzyltrimethylammonium chloride (BTEAC) in two phase condition instead of using triton B in dry pyridine (eq. 3). Thus, oxygen gas was introduced to a solution of BTEAC, 9-hexylfluorene and trace of 10*N*-NaOH in a mixture of pyridine/toluene (2:3) with

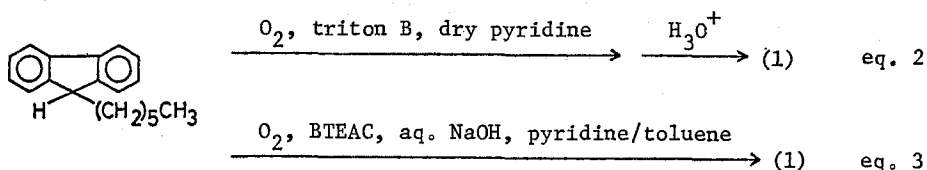


Fig. 2.

vigorous stirring at r.t. for 4 h. After evaporation of the solvent, the concentrate was acidified and 9-hydroperoxy-9-hexylfluorene was isolated by column chromatography. From this experiment, the hydroperoxide was obtained with 89% chemical yield.










An important point of this system was the use of small amount of aq. NaOH solution with very high concentration otherwise the hydroperoxidation was unsuccessful under typical PTC conditions where comparable amount of water to organic solvent is used. The advantages over the triton B method are that the present procedure did not require dry solvent, dry oxygen gas and low temperature. Moreover, oxygen gas could be replaced by air affording the hydroperoxide in 77% yield.

This result suggested that both the PTC-catalyzed hydroperoxidation of 9-hexylfluorene (eq. 3) and the PTC-catalyzed Weitz-Scheffer epoxidation⁷⁾ (eq. 1) must be conducted at the same time by use of the one PTC in a single flask. To test this possibility, oxygen gas was introduced for more than 20 h to a solution of cyclohexenone as a substrate of the epoxidation, 9-hexylfluorene as a precursor of the hydroperoxide, BTEAC and small amount of 10*N*-NaOH in a mixture of benzene and pyridine (2/3).

Unexpectedly, however, cyclohexenone 2,3-epoxide with only 27% c.y. was produced mostly leaving the starting materials. Search for the cause of this low yield revealed that existence of cyclohexenones in the reaction mixture strongly

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Table 1. Inhibition of Peroxidation of 9-Hexylfluorene by Cycloalkenones*











run	cycloalkenone	(cycloalkenone) (9-hexylfluorene)	chem. yield of 9-hexyl- fluorenyl hydroperoxide**
1		0	93%
2		0.18	47
3		0.53	24
4		1.00	16
5		1.00	11
6		1.00	13
7		1.00	27
8		1.00	34
9		1.00	2

*) In runs 1~4 and 5~9, 0.05 and 0.02 mol equivalent of benzyltriethylammonium chloride to 9-hexylfluorene were used, respectively.

***) The hydroperoxide content was determined by iodometry.

depressed the formation of the hydroperoxide even in a catalytic manner to some extent (Table 1). For example, as run 2 shows, yield of the hydroperoxide decreased to 47% from 93% (run 1) in the presence of 18% mol of 2,3-cyclohexenone to 9-hexylfluorene. With equivalent mole of cyclohexenone, the formation of the hydroperoxide dropped to 16% (run 4). Furthermore, no addition product from the possible 1,4-nucleophilic attack of fluorenyl anion to cyclohexenones was detected at all, and most of 9-hexylfluorene was recovered.⁸⁾ Taking account of this inhibitory action of cyclohexenones, a possible route for effective hydroperoxidation and epoxidation in a single pot may be an addition of cyclohexenone after completion of the hydroperoxide formation. Thus, as described above, 9-hexylfluorene was oxidized first to the hydroperoxide (1) according to eq. (2), and then the substrate was added to the oxidation mixture followed by stirring for 24 h at room temperature. As shown in Table 2, it was found that the corresponding epoxyketones were obtained in reasonable yield after usual work-up. On the other hand, when air was used instead of oxygen gas, the yields reduced to 15~75%. However, removing of carbon dioxide from the air by bubbling it through aq. NaOH improved the

Table 2. Peroxidation and Epoxidation in a Single Pot with Benzyltriethylammonium Chloride

run	substrate	epoxide	% chem. yield*		
			O ₂	air	air without CO ₂
1			100	48	100
2			100	60	100
3			100	75	100
4			72	57	62
5			71	15	63

*) conversion yield by v.p.c.

conversion yield to the same level as with oxygen gas. As seen in runs 4 and 5, 4,4-dimethylcyclohexanone and vitamine K3 afforded relatively low conversion yields (60~70%). Although the reason for the former may be ascribed to steric hindrance by the two methyl groups, for the latter, it is unknown.

As an extension of the above oxidation system, asymmetric epoxidation of cyclohexenones was undertaken by use of chiral bis(PTC) (2a or 2b) under the same condition except for the temperature of the epoxidation. As shown in Table 3, the optically active epoxides were obtained with the chemical yield ranging over 13~85%. Cyclohexenone afforded (2*S*, 3*S*) cyclohexenone 2,3-epoxide with 44 (run 1) and 54 (run 6) % e.e. by use of (2a) and (2b) respectively.⁹⁾ On the other hand, for 5,5-dimethylcyclohexanone (runs 2 and 7) and 3-methylnaphthoquinone (runs 3 and 8), the stereoselectivities were found to be small whereas reasonable chemical yields (57~82%) were observed. The other substrates, 4-methylcyclohexenone (runs 4 and 9) and 4,4-dimethylcyclohexenone (runs 5 and 10) also afforded the optically active 2,3-epoxyketones whose optical purities and absolute configuration were unknown.

Thus, it was demonstrated that chiral PTC's which have been used as catalyst for asymmetric epoxidations⁵⁾ were also feasible for the hydroperoxidation of 9-hexylfluorene and the both processes could successively be performed in a single flask to give optically active epoxides. Although the stereoselectivities were unsatisfactory as a method for asymmetric synthesis, the present study constitutes a first example for utilization of molecular oxygen and preparation of chiral epoxide in a single flask by use of chiral PTC. The use of PTC constitutes one of the most important techniques of organic chemistry¹⁰⁾ and a number of asymmetric syntheses using chiral PTC have also been reported. It appears, however, that examples of very

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Table 3. Asymmetric Epoxidation with Chiral PTC (2a) and (2b)

run	X	substrate	product	react. temp.	% chem. yield	% e.e.	configuration
1	Br			-20°C	34	44	2 <i>S</i> , 3 <i>S</i>
2	Br			-20	57	9	—
3	Br			-20	76	4	2 <i>S</i> , 3 <i>R</i>
4	Br			r.t.	82	(-24.8°)*	—
5	Br			r.t.	51	(-17.1°)*	—
6	Cl			-20	85	54	2 <i>S</i> , 3 <i>S</i>
7	Cl			-20	80	7	—
8	Cl			-20	82	1	2 <i>S</i> , 3 <i>R</i>
9	Cl			r.t.	68	(-29.4°)*	—
10	Cl			r.t.	13	(-19.9°)*	—

*) Optical rotation at 578 nm in methylene chloride

high stereoselectivity have been rather scarce and the selectivity seems to depend subtly on the structure of PTC^{5,11)} as well as of reactant,^{5,12)} solvent,^{9,13)} and type of reaction.¹²⁾ In the present study, further variation of PTC structure might be of prime importance so far as concerning with improvement of the stereoselectivities.

EXPERIMENTAL

Optical rotations were taken on a Perkin-Elmer 241 polarimeter. VPC were on a Shimadzu GC-4CM and a Varian Aerograph Model 920 for preparative scale chromatography. Preparation of chiral bis(PTC) (2) was described in our previous study.⁵⁾ 4,4-Dimethyl-2,3-cyclohexane,¹⁵⁾ 4-methyl-2,3-cyclohexane,¹⁶⁾ and 5,5-dimethyl-2,3-cyclohexanone¹⁷⁾ were prepared according to the literature methods.

Preparation of the hydroperoxide (1) under phase transfer condition.

Into a solution of benzyltriethylammonium chloride (38 mg, 0.17 mmol), 9-hexylfluorene (1.3 g, 5.2 mmol) and 10*N*-NaOH (124 μ l) in a mixture (17 ml) of

pyridine/toluene (2/3), oxygen gas was bubbled with vigorous stirring for 4 h. After evaporation of the solvent, the residue was purified by chromatography (silica gel, CH₂Cl₂/hexane (5/1)). Chem. yield, 1.30 g (89%). When air was used instead of oxygen gas, the hydroperoxide was obtained in 77% yield.

Inhibition of hydroperoxidation of 9-hexylfluorene by cyclohexanones.

The hydroperoxidation was conducted under the same condition described above in the presence of varying amount cyclohexanones as shown in Table I. After the reaction, the hydroperoxide contents were determined by iodometry.

Hydroperoxidation and subsequent epoxidation in a single flask.

After the hydroperoxidation of 9-hexylfluorene (0.15 g, 0.59 mmol) in pyridine/toluene (2/3) (5 ml) for 2 h in the presence of benzyltriethylammonium chloride (5.5 mg, 0.024 mmol) and 10*N*-NaOH (36 μl), alkyl cyclohexenone (0.45 mmol) was added and stirred overnight at room temperature. The chemical yield was determined by gas chromatography (5%-XE-60, 2 m, 140°C). Hexane (20 ml) was added with shaking to the reaction mixture and filtered. The filtrate was concentrated and the residue was distilled at 20 mm by Kugel Rohr apparatus to separate epoxide containing fraction from 9-hexylfluorenol and benzyltriethylammonium chloride. From the distillate, epoxide were isolated pure by preparative VPC (5%-XE-60, 2 m, 160°C). Proton NMR spectra confirmed the purity and structural integrity of the epoxide.⁹⁾

Hydroperoxidation and asymmetric epoxidation in a single flask.

The same procedure as described above was conducted in the presence of bis(PTC) (2) instead of benzyltriethylammonium chloride. Since the catalytic activity of the bis(PTC) seemed to be lower than benzyltriethylammonium chloride, additional bis(PTC) of the same amount was supplemented before addition of cyclohexenone. The epoxide was isolated pure as described above and the optical purity was determined from its optical rotation.⁹⁾

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