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Stereoselective Syntheses of cis-Cyanooxiranes by Reaction of α-Bromoketones with Cyanide Ion Adsorbed onto Hemin-Copolymer

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Summary : Sterically controlled addition reactions of cyanide to α-bromoketones by using CN-modified hemin-copolymer in nonaqueous system were carried out, and cis-cyano-oxiranes were obtained selectively.

Iron-Porphyrin complex is a kind of tetrapyrrole derivative containing large π electron system and shows aromatic property. The axial coordination site of porphyrin is an interesting reaction field for various organic reactions. In the previous study from this laboratory, copolymers containing hemin (1) were synthesized and the CN-combined hemin-copolymer has been used as polymer-reagents in asymmetric syntheses of amino acids by addition of cyanide to the Schiff bases1). The results obtained indicate that the addition reactions using the CN-modified hemin-copolymer were sterically controlled by the porphyrin ring.

In this study, by the use of CN-modified hemin-copolyer(1), stereoselective syntheses of cis-cyanooxiranes from α-bromoketones in nonaqueous system were carried out. It was found that the steric control in this reaction using CN-modified hemin-copolymer was much more effective than the case using CN-bound anion exchange resin (Amberlyst A26)(2) under the same conditions or using KCN in DMF.

Hemin-copolymer(1) was prepared by suspension copolymerization of hemin, divinylbenzene and 2-methyl-5-vinylpyridine in aqueous organic solvent2). The hemin-copolymer was controlled to from in beeds like uniform size (average diameter=250μm). The measurement of the surface of the beeds showed that the hemin-copolymer was macroporous and the hemin content was 0.1 mmol/g, and the degree of crosslinkage is 50%. The hemin-copolymer (1eq) was treated with aqueous solution of potassium cyanide (20eq) at pH9.0 at room temperature for overnight, and the CN-modified hemin-copolymer was filtered off and lyophilized. The CN content of the polymer was determined by the method described in the previous study[2]. α-Bromoketones, commercially obtained, were twice distilled under reduced pressure or recrystallized immediately befor use. α-Bromoketones used were 2-bromo-2-phenylacetophenone (3) and 3-bromo-2-butanone (4).

The typycal procedure for the synthesis of cyanooxirane was as follows : CN-combined hemin-copolymer(1) (1mmol as CN^-) and α-bromoketone(0.25mmol) were added in dichloromethane and it was kept at 20°C for 4h. The progress of the reaction was checked by thin layer chromatography. After the reaction was over, hemin-copolymer was removed by filtration and was washed with ether. The combined organic solution was evaporated under reduced pressure. The chemical yield of cyanooxirane was determined by gas chromatography (G.C.) with the authentic sample[3,4]. And the ratio of cis- to trans-isomer was determined by G.C. analysis and NMR spectroscopy[3,4].

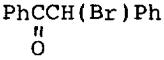
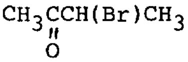
The results are summerized in Table 1. In the case of KCN in DMF and CN-bound Amberlyst A26(2) in dichloromethane, the ratio of cis- to trans-isomer was approximetely 50 : 50. When the CN-modified hemin-copolymer was used, cis-cyanooxiranes were produced predominantly. This tendency by the use of substrate 3 was similar to that of 4.

It has been reported that the reaction of 3 dissolved in dichloromethane with aqueous KCN solution adsorbed on solid adsorbent (silica gel or alumina) gave stereoselectively cis-2,3-diphenyl-2-cyanooxirane. They explained that the selectivity was due to the structural restriction of bromocyanohydrin anion owing to interaction between phenyl group and solid adsorbent[5].

In general the reaction pathway of cyanooxirane synthesis from α-bromoketone with CN^- ion involves two steps. The first step is the formation of bromocyanohydrin anion by addition of CN^- to C=O bond, and the second step is the formation of epoxy ring by intramolecular nucleophilic attack of bromocyanhydrin anion to α-carbon atom. It has been considered that the formation of epoxy ring in DMF and dichloromethane proceeds with Sn2 mechanism. Therefore, it is reasonable to assume that the cis- or trans- determining factor is the probability of CN addition to re- or si-face of α-bromoketone. From the result in Table 1., when KCN and Amberlyst A26(2) were used, the attack of CN^- to carbonyl carbone of α-bromoketone occured from re- and si- faces in the same probability. On the other hand, when hemin-copolymer(1) was used, CN^- addition took place predominantly to re- or si- face of α-bromoketone. In the hemin-copolymer, cyanide combined with the hemin site with ionic and also with coodination bond. Therefore, the direction of CN^- addition was sterically controlled by the presence of porphyrin ring.

A possible reaction pathway is shown in Fig.1. Racemic α-bromoketones were used as the substrate. In Fig. 1., (R)-isomer was used in this explanation and the substrate have re and si face (Fig.1-b), and the conformation of the substrate could be the dipolar model (Fig.1-c). The

Table 1. Stereoselective Syntheses of cis-Cyanooxiranes by Reaction of α-Bromoketones with Cyanide Ion Adsorbed onto Hemin-copolymer[a].

			Chemical Yield[c] of Oxirane	Composition[d] (%)	
Substrate	Reagent[b]	Solvent	(%)	cis	trans
 $\mathrm{Ph}\underset{\substack{\parallel \\ \mathrm{O}}}{\mathrm{C}}\mathrm{CH(Br)Ph}$	1	CH_2Cl_2	91	98	2
(3)	2	CH_2Cl_2	72	48	52
	KCN	DMF	65	49	51
 $\mathrm{CH_3}\underset{\substack{\parallel \\ \mathrm{O}}}{\mathrm{C}}\mathrm{CH(Br)CH_3}$	1	CH_2Cl_2	90	87	13
(4)	2	CH_2Cl_2	76	50	50
	KCN	DMF	67	47	53

a) 20°C, 4h, bromoketone : CN^- = 0.25 : 1 mmol/10ml solvent.
b) 1 : CN-bound hemin-copolymer ; 2 : CN-bound Amberlyst A26.
c) The chemical yield was determined by G.C. analysis.
d) Cis and trans ratio was determined by G.C. analysis and NMR.
NMR (methyne proton), 3, cis:4.73ppm, trans:4.16ppm[3],
4, cis: q, 3.16ppm, trans: q, 3.51ppm[4].

experimental results indicate that the substrate approaching to the hemin site with the least sterically hindered side. Thus, cyanide ion attack to the face (si-face) having the smallest substituent (H) of the substrate, as shown in Fig. 1-d. The resulting bromocyanohydrin anion (Fig. 1-e) gives cis-cyanooxirane by anti-elimination (Fig. 1-f). This reaction pathway obeys the Cornforth's rule.

Stereoselective syntheses of cis-cyanooxirane was carried out by the reaction of α-bromoketone with CN-modified hemin-copolymer. It could be considered that the reaction proceed strongly diastereoselective way. The other applications of organic reaction using the modified hemin-copolymer are under way.

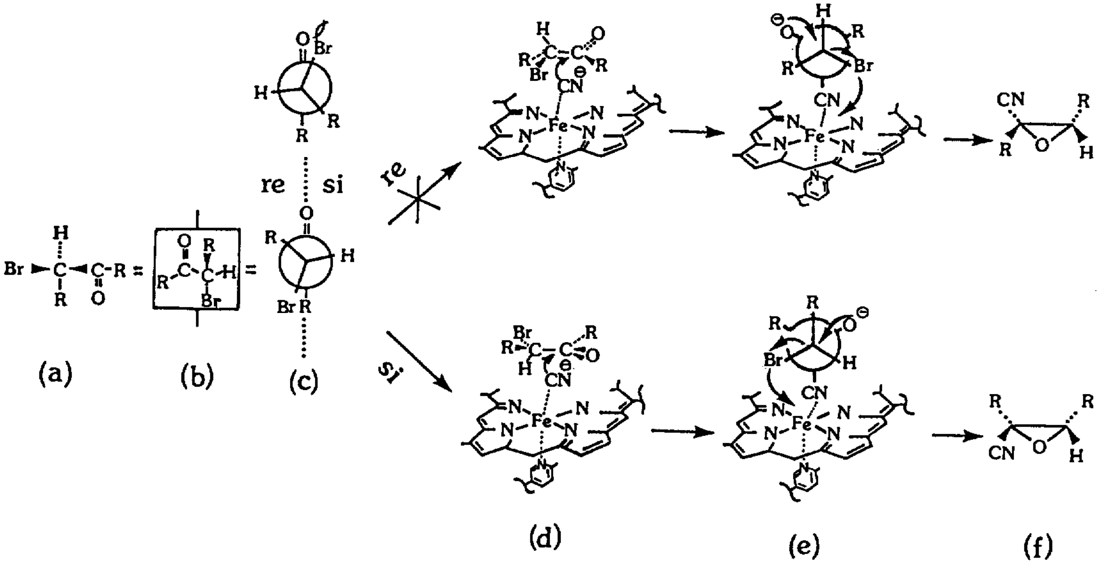


Fig. 1. A Possible Reaction Pathway of the Stereoselective Syntheses of cis-Cyanooxiranes by Using CN-Modified Hemin-Copolymer.

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