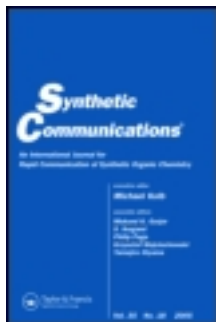


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**HIGHLY REGIO- AND STEREOSELECTIVE
SYNTHESIS OF β -HALOHYDRINS FROM
EPOXIDES CATALYZED WITH
CERIC AMMONIUM NITRATE**

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Abstract: Ce(IV) as ceric ammonium nitrate can effectively catalyze ring opening of epoxides with halides under very mild conditions and easy procedure to give the corresponding β -chloro- and β - bromohydrins in excellent yields. The reactions occur with both substituted and unsubstituted quaternary ammonium halides and with high regio- and stereoselectivity. The reaction of optically active styrene oxide with chloride ion was found to be highly stereospecific and afforded the corresponding β -halohydrin in 96% ee.

Epoxides are versatile intermediates in organic synthesis and their nucleophilic ring opening reactions with a variety of nucleophiles have been

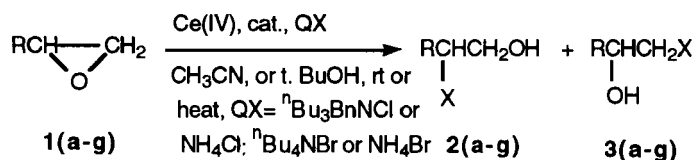
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extensively studied.¹ Due to the considerable importance of vicinal halohydrins in organic synthesis^{2,3} and the low regioselectivity in the conventional method of the addition of hypohalous acids to unsymmetrical olefins,⁴ special interest has been shown to develop new methods with higher regioselectivity. Ring opening of epoxides with different halogenated agents was considered to be an important synthetic method to obtain vicinal halohydrins⁵ and many reagents have been introduced for this purpose. However, as usual for every reagent, these methods are not always fully satisfactory and suffer from disadvantages such as acidity,^{6,7,8} handling and in situ preparation of reagents,⁹⁻¹² low regioselectivity,^{7,9,10,13a,b} non-catalytic nature of the reagents⁸⁻¹⁰ and relatively long reactions time.^{10,13a}

We have already reported the use of Ce(IV) as catalyst for some nucleophilic ring opening reactions of epoxides and thiiranes¹⁴. In this paper we wish to report that Ce(IV) as commercially available ceric ammonium nitrate (CAN) can effectively catalyze ring opening reactions of epoxides with chloride and bromide ions as their quaternary ammonium salts in dry acetonitrile or in t.butanol and as unsubstituted ammonium salts in t.butanol to produce the corresponding β -halohydrins in high yields and with high regio- and stereoselectivity.

Scheme 1



R or Epoxide: (a) R = Ph (b) R = PhOCH₂ (c) R = (CH₃)₂CHOCH₂ (d) epoxide=cyclohexene oxide (e) CH₂ = CHCH₂OCH₂ (f) R = ClCH₂ (g) R = CH₃

Reactions of different classes of epoxides carrying activated and deactivated groups with chloride ion as its tri-*n*-butyl benzyl ammonium and with bromide as its tetra-*n*-butyl ammonium salt in acetonitrile were performed in the presence of Ce(IV) as ceric ammonium nitrate. The reactions took place either at room temperature or under reflux conditions and a catalytic amount of Ce(IV) as CAN was required to produce the corresponding β -halohydrins in high yields. The results are shown in Table 1.

The reaction of styrene oxide with metal halides in most of the reported methods suffers from low regioselectivity and the major product is formed from attack of halide ion to the β carbon of the epoxide ring, except in a few reactions in which acidic conditions are employed. Under acidic conditions, the product obtained from α attack is usually the major product but in most cases a low regioselectivity is reported.^{7,8,13b} In our case, the ring opening of styrene oxide occurs from attack on the α carbon of the epoxide ring with excellent yield and regioselectivity. In this study, the possibility of using ammonium chloride and bromide as the source of halide ions was also studied in *t*. butanol. Here again, the reactions were found to be highly regioselective and the corresponding halohydrins were obtained in excellent yields. A recent report on the use of metal salts for conversion of epoxides to halohydrins was unsuccessful with both substituted and unsubstituted ammonium halides.^{13a}

The high regioselectivity observed in these reactions is controlled by electronic effects and attack of nucleophile occurs on that carbon atom which can effectively stabilize the developing positive charge. In case (g) in which electronic and steric effects are counter balanced, minor amounts of product of α - attack were also obtained (Table 1).

					Found	Reported
0.3	A/CH ₃ CN	3	2a (X=Cl)	85%	114-118/6	106-118
0.2	A/t.BuOH	0.33	2a (X=Cl)	98	-	-
0.2	B/t.BuOH	3	2a (X=Cl)	54+46% diol	-	-
0.3	C/CH ₃ CN	0.3	2a (X=Br)	92	36-37	38 ¹⁷
0.2	C/t.BuOH	0.5	2a (X=Br)	98	-	-
0.2	D/t.BuOH	2	2a (X=Br)	95	-	-
0.3	A/CH ₃ CN	1	3b (X=Cl)	93	136/8	112/114
0.2	A/t.BuOH	0.3	3b (X=Cl)	97	-	-
0.2	B/t.BuOH	0.3	3b (X=Cl)	93	-	-
0.4	C/CH ₃ CN	1	3b (X=Br)	98	160-161/15	167-9/15
0.3	C/t.BuOH	0.3	3b (X=Br)	95	-	-
0.3	D/t.BuOH	0.3	3b (X=Br)	97	-	-
0.3	A/CH ₃ CN ^{IV}	0.85	3c (X=Cl)	95	87-88/20	180-182

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0.2	C/t.BuOH	5	3 c(X=Br)	92	-	-
0.2	D/t.BuOH	6	3 c(X=Br)	90	-	-
0.3	A/CH ₃ CN	1	trans 2-chlorocyclohexanol	98	71/7	93/26 ²
0.2	A/t.BuOH	2	trans 2-chlorocyclohexanol	95	-	-
0.2	B/t.BuOH	3	trans 2-chlorocyclohexanol	95	-	-
0.3	C/CH ₃ CN	3	trans 2-Bromocyclohexanol	98	86/10	88-90/
0.2	C/t.BuOH	2	trans 2-Bromocyclohexanol	96	-	-
0.2	D/t.BuOH	3	trans 2-Bromocyclohexanol	92	-	-
0.3	A/CH ₃ CN	1	3 e(X=Cl)	93	103-105/25	107-10
0.3	A/t.BuOH	0.3	3 e(X=Cl)	95	-	-
0.3	B/t.BuOH	2	3 e(X=Cl)	96	-	-
0.3	C/CH ₃ CN	3	3 e(X=Br)	99	112/20	-
0.3	C/t.BuOH	0.5	3 e(X=Br)	94	-	-

0.2	A/t.BuOH	1.5	3 f (X=Cl)	95	-	-
0.2	B/t.BuOH	4	3 f (X=Cl)	96	-	-
0.3	C/CH ₃ CN	3	3 f (X=Br)	90	95/15	95-98
0.2	C/t.BuOH	1.5	3 f (X=Br)	96	-	-
0.2	D/t.BuOH	4	3 f (X=Br)	96	-	-
0.3	A/CH ₃ CN	3	2 g (X=Cl)	70+18% <i>C_β</i> attack	53-54/29	53-53
0.2	A/t.BuOH	2	2 g (X=Cl)	92	-	-
0.2	B/t.BuOH	2	2 g (X=Cl)	90	-	-
0.3	C/CH ₃ CN	3	2 g (X=Br)	80+10% <i>C_β</i> attack	58-59/10	62.8-6
0.2	C/t.BuOH	2	2 g (X=Br)	93+3% <i>C_β</i> attack	-	-
0.2	D/t.BuOH	2	2 g (X=Br)	89+5% <i>C_β</i> attack	-	-

A: benzyl ammonium chloride. B: ammonium chloride. C: tetra-n-butyl ammonium bromide. D: ammonium bromide. The samples are separated and compared with authentic samples.

isolated product.

dition.

Although the ring opening reactions of epoxides with halides have been extensively studied, the results of this type of reaction on optical active epoxides is very rare. Very recently, ring opening reaction of chiral styrene oxide with halides supported on SiO_2 has been reported,^{13b} but the regio- and enantioselectivity of the reaction is not satisfactory. The total yield of the reaction is equal to 81% with the formation of the products of β and α attack in 47% and 53% respectively. The enantiomeric excess of the product of α attack is reported to be 32%.

With our method, the reaction of (R)-(+)-styrene oxide with chloride ion as tri-n-butyl benzyl ammonium chloride and in the presence of 0.3 molar equivalent of CAN was studied in both solvents. The reaction in t.butanol showed low enantiomeric excess (6% ee), but the reaction in acetonitrile was found to be highly regio- and enantioselective and the corresponding halohydrin was obtained in 96% ee. The optical purity of the product was obtained by comparison of the optical rotation of the product with the reported data according to the literature. The results of this study are shown in Scheme 2 and Table 2.

In order to show the advantages and disadvantages of this method, the results obtained from the reaction of styrene oxide with halides in the presence of Ce(IV) are compared with some of those reported in the literature (Table 3).

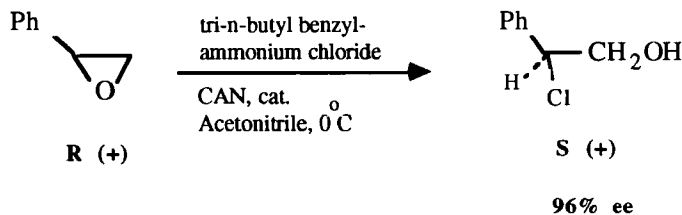
Scheme 2

Table 2. Reaction of R (+) styrene oxide with three molar equivalents of tri-*n*-butyl benzyl ammonium chloride in the presence of CAN.

Solvent	CAN/Epoxyde	Time(h)	Temp(°C)	Yield% ^I (ee%) ^{II}
t.Butanol	0.2	1	25	92(6)
CH ₃ CN	0.3	3	25	85(43)
CH ₃ CN	0.3	7	0	97(96)

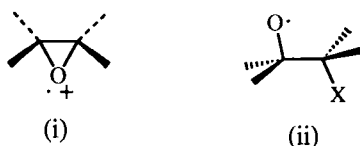
I: Yields refer to isolated product.

II: The enantiomeric excess was obtained by comparison of the optical rotation of the obtained product with that reported in the literature²⁶

Table 3. Reaction of Styrene Oxide with Different Reagents.

Reagent or Catalyst	Halide Ion	Time (h)	%Product	% α Attack	% β Attack
Li ₂ CuCl ₄ ¹⁰	-	5	83	75	25
LiX/THF/AcOH ⁷	I	0.75	87	66	34
LiX/Amberlyst ^{8a}	Cl	-	-	90	10
LiX/Amberlyst ^{8a}	Br	-	-	90	10
Li ₂ NiBr ₄ ⁹	-	2	97	30	70
SnCl ₂ ^{8b}	-	-	77	77	-
LiX/SiO ₂ ^{13b}	Cl	13 days	52	62	38
Ce(IV)	Cl	0.33	98	98	-
Ce(IV)	Br	0.5	99	99	-

Although the exact mechanism of the reaction is not clear, on the basis of our previous observations on the reaction of Ce(IV) with epoxides and especially thiiranes¹⁴ and a recent report on the use of Ce(IV) as CAN for deprotection of tert-butoxycarbonyl group,²¹ the possibility of a one- electron transfer reaction between epoxide and Ce(IV) can not be ruled out. In this mechanism the formation of an epoxonium radical cation (i) followed by attack of halide ion can produce the corresponding halohydrin.



The catalytic nature of the reaction can be shown by regeneration of Ce(IV) from the reaction of Ce(III) and the developing alkoxy radical (ii) in this reaction. Regeneration of Ce(IV) from Ce(III) in the reaction of hydroxy radical and Ce(III) has been shown to occur very rapidly.¹⁵ In support of a radical type mechanism, the reaction of styrene oxide and chloride ion was performed in the presence of Ce(IV) and excess of acrylamide. A large amount of polyacrylamide was obtained with considerable decrease in the reaction rate.

Experimental

Products were characterized by comparison of their physical data, i.r , n.m.r and mass spectra with those prepared according to literature procedures. All yields refer to isolated products. Infrared spectra were recorded on a Perkin Elmer IR-157 G and a Perkin Elmer 781 spectrometer. NMR spectra were recorded on a Hitachi, R-2413, 60 MHz or Varian XL-100 spectrophotometer. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX . The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates or GLC on a Shimadzu GC-8A instrument with a flame ionization detector using a column of 15% carbowax 20M chromosorb-w acid washed 60-80 mesh. Chemicals were purchased from Fluka and Merck chemical companies. Products were separated and purified by different chromatography techniques or vacuum distillation.

General Procedure: Ceric ammonium nitrate (2 - 4 mmol) was added gradually to a mixture of epoxide (10 mmol) and the appropriate quaternary ammonium halide (30 mmol) in dry acetonitrile or t.butanol (30 mL). The mixture was stirred for the specified time and at an appropriate temperature according to Table 1. The progress of the reaction was monitored by glc. The solvent was evaporated, water (30 mL) was added, and the mixture was extracted with ether (3 x 60 mL). Evaporation of the solvent followed by column chromatography on a short column of silica gel afforded the pure product.

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