Epoxidation by sodium chlorite with aldehyde-promoted chlorine dioxide formation

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ABSTRACT

An improved method is described for selective room temperature epoxidation of alkenes by sodium chlorite in a solvent mixture of ethanol, acetonitrile, and water buffered at pH 7. In addition, the use of aldehydes as promoters in chlorite oxidations is described for the first time. The amount of sodium chlorite, the solvent mixture, and the addition of formaldehyde as a practical promoter were optimized. Styrene was used as a test substrate in the optimization studies and the generality of the method was assessed by using a variety of nucleophilic and electrophilic substrates. Yields up to 89% were obtained with styrene and other nucleophilic alkenes are readily converted into epoxides.

The uses of sodium chlorite in synthetic organic chemistry have been reviewed.[1] Under certain conditions, the byproducts of chlorite oxidations, in particular hypochlorous acid, can lead to the formation of other reactive chlorine species, such as chlorine dioxide (ClO_2). Chlorine dioxide is a stable free radical that functions as a one-electron oxidant in reactions with reducing substrates, such as amines,[2–7] sulfides,[8] and phenols.[9–13] A radical mechanism has been proposed for the reactions of ClO_2 with allylic and benzylic substrates.[14–16] In addition, it has been proposed that epoxides can be formed in ClO_2 reactions with alkenes via a radical addition–elimination mechanism.[14,17] Although ClO_2 has potentially useful properties as a selective radical reagent for organic transformations, it must be produced immediately prior to its use via direct synthesis since it is an explosive gas[18] and is unstable when stored in solution. Sodium chlorite, on the other hand, is readily obtained, relatively stable in storage as a strongly oxidizing solid, and can serve as a source of ClO_2 in situ under appropriate conditions.

Geng et al.[19] reported sodium chlorite as an oxidant for epoxidation of alkenes to their corresponding epoxides in an acetonitrile/water mixture at 55–65 °C. The authors found that chlorine dioxide is responsible for the epoxidation of alkenes and that chlorite generates chlorine dioxide at the elevated reaction temperature. Previously, Kolar and Lindgren[17] had observed styrene oxide as a product of the ClO_2 reaction with styrene but their acidic conditions did not favor epoxide formation and only low yields were obtained.

We report herein an improved method for the selective, room temperature epoxidation of alkenes by sodium chlorite in a solvent mixture of ethanol, acetonitrile, and water buffered at pH 7. In addition, we describe the use of aldehydes as promoters for the first time. In this investigation we have optimized the amount of sodium chlorite, the solvent mixture, and the use of formaldehyde as a practical and simple promoter. Styrene was used as a test substrate in the optimization studies and the generality of the method was assessed with a variety of nucleophilic and electrophilic substrates. By using high concentrations of chlorite ion, neutral pH conditions, and selected solvent combinations, we are able to obtain high conversion levels (99+ %) and epoxidation selectivities up to 89% at room temperature for styrene.

Table 1 summarizes a survey of results for the epoxidation of styrene by sodium chlorite under various conditions. Initially, the room temperature epoxidation of styrene was carried out by using different concentrations of sodium chlorite in ethanol/water (3:1, v/v; 100 mM styrene, 15 mL ethanol, 5 mL water (phosphate buffer, pH 7, 100 mM)). Neutral pH conditions were used to reduce hydrolysis of the desired epoxide product. Yields increased to 88% at the higher concentrations of sodium chlorite (as a result of both higher conversions and selectivities), and based on these results, 10 equiv of chlorite was used in subsequent experiments. In all reactions, there was a significant induction period before the reaction achieved the maximum rate. With 1.0 M chlorite, the induction period is ~1 to 1.5 h and the maximum reaction rate is observed at ~2 h (Fig. 1). As the reactions progress, we observe the accumulation of dissolved ClO_2, as observed by Kolar and Lindgren[17] and Geng et al.[19]

We also screened various solvent combinations (Table 1). No reaction was observed in pure water, presumably due to the insolubility of styrene and/or slow formation of ClO_2. Among the

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Table 1
Solvent and temperature effects in epoxidation of styrene by sodium chlorite

[NaClO$_2$] (M)	Solvent[a]	Runtime (h)	Reaction temp (°C)	Yield of epoxide[b] (%)
0.3	EtOH/H$_2$O	7	25	60
0.5	EtOH/H$_2$O	6	25	70
1.0	EtOH/H$_2$O	5	25	88
1.5	EtOH/H$_2$O	4.5	25	88
1.0	MeOH/H$_2$O	5	25	81
1.0	1-PrOH/H$_2$O	8	25	80
1.0	1-BuOH/H$_2$O	22	25	64
1.0	i-PrOH/H$_2$O	18	25	64
1.0	t-BuOH/H$_2$O	22	25	70
1.0	Acetonitrile/H$_2$O	24	25	60
1.0	EtOH/H$_2$O (4:1)	5	25	83
1.0	EtOH/H$_2$O (2:1)	4	25	80
1.0	EtOH/H$_2$O (1:1)	3	25	76
1.0	EtOH (100%)	20	25	82
1.0	EtOH/H$_2$O	20	15	83
1.0	EtOH/H$_2$O	2	35	81

[a] Solvent/water ratio is 3:1, unless otherwise noted. Water is buffered to pH 7, 100 mM phosphate buffer. [styrene] = 100 mM.
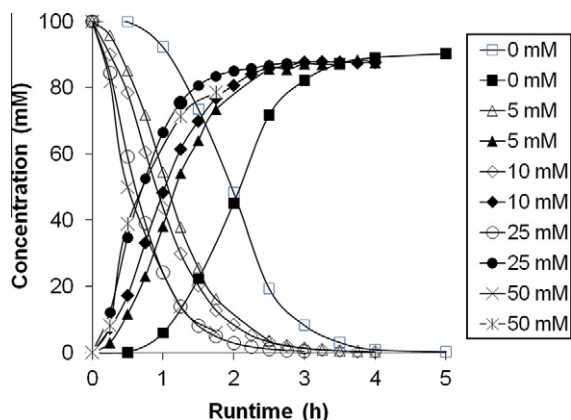[b] Yields are based on GC analysis and are equal to conversion × selectivity.

Figure 1. Kinetics of epoxidation of styrene to styrene oxide using sodium chlorite (1.0 M in 3:1 ethanol/H$_2$O pH 7 phosphate buffer) with varying concentrations of formaldehyde (legend). Open markers: styrene; filled markers: styrene oxide. Addition of formaldehyde up to a final concentration of 25 mM reduces the induction period but does not reduce the selectivity for the epoxide product.

solvent systems we studied, ethanol/water resulted in the highest yield, with 100% conversion and 88% selectivity. Higher molecular weight alcohols maintained relatively high conversions (at longer reaction times) but produced significantly lower selectivities.

We also tested the influence of the solvent to water ratio and noted that 3:1 ethanol/water gives the highest yield. At ethanol/water ratios of less than 2:1, yields and selectivities were <80%. Relatively small changes in selectivity occurred over the range of 15–35 °C but the required reaction time decreased significantly at 35 °C.

Although chlorite is the ultimate source of oxidant in the epoxidation reaction, the mechanism of chlorite epoxidation is believed to involve the intermediate formation of chlorine dioxide and a chain reaction as described by Kolar and Lindgren.[17] We observed that the induction period can be eliminated by direct addition of chlorine dioxide (~15 mM), reducing the reaction time substantially. However, synthesis of pure chlorine dioxide solutions is time-consuming and must be done carefully to avoid explosions and the resulting stock solutions have limited storage lifetimes. We, therefore, sought a convenient method for producing chlorine dioxide in situ by rapid conversion of a small portion of the chlorite to chlorine dioxide. Although oxidants such as bromine can be

added to yield ClO$_2$ and initiate the reaction, we have found that the addition of aldehydes is a particularly convenient method for producing the requisite amounts of chlorine dioxide in situ. In particular, formaldehyde is an attractive promoter because the end product in its oxidation by a large excess of chlorite is carbon dioxide.[20] In this way, the promoter byproduct is effectively removed from the reaction mixture during the reaction and does not interfere with the isolation of product. The oxidation of aldehydes by chlorite ion is well known[21] and a few recent studies have investigated the mechanism of ClO$_2$ formation.[20,22] In the absence of substrate, ClO$_2$ is produced in a few minutes via the reaction of chlorite with formaldehyde in our reaction conditions.

The promotional effect of HCHO was investigated for styrene epoxidation using various concentrations of the promoter (Fig. 1). The induction period is reduced with the increasing amounts of promoter and essentially eliminated at 25 mM HCHO. It is noteworthy that the addition of HCHO minimized or effectively eliminated the initial induction period but did not reduce the maximum rate of the reaction.

Along with HCHO, we have also checked other aldehydes, such as glyoxal, benzaldehyde, and glucose and the results are presented in Table 2. With the exception of glucose, which reacts slowly with chlorite ion,[23,24] there is a significant decrease in the required runtime of the reaction with the addition of small amounts of these aldehydes due to the decrease of the induction period. The ultimate yields are generally almost unchanged but addition of the highest amounts of aldehyde (50 mM) results in reduced styrene oxide yield, presumably due to the rapid generation of large amounts of HOCl, which reacts with styrene to produce chlorinated byproducts.[17] Based on these results, we settled on a standard of 25 mM for the aldehyde promoter concentration.

The convenience and relatively high yields of the aldehyde-promoted reaction led us to examine a variety of alkenes to assess the generality of the method. Since ethanol/water is not a good solvent for many substrates, we have broadened the applicability of the method by replacing some of the ethanol co-solvent with acetonitrile. The effect of the solvent change on the styrene prototype reaction is nil and we obtained an 89% styrene oxide yield in 5 h with an acetonitrile/ethanol ratio of 2:1. Consequently, the optimal reaction system was composed of 10 equiv of sodium chlorite in acetonitrile/ethanol/pH 7 aq buffer (2:1:1, by volume) promoted by 25 mM HCHO at room temperature (25 °C).

The method was tested on substituted aliphatic and aromatic alkenes (Table 3) under the optimized conditions. The reactions were done with and without formaldehyde promoter for comparison. For this wide variety of alkenes, the rates, conversions, and selectivities were in general fair to very good for the promoted reactions but tend to be better for nucleophilic alkenes (α-methylstyrene was an exception, where the increased rate in the
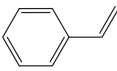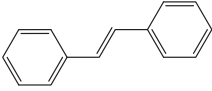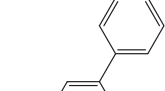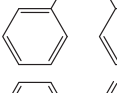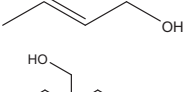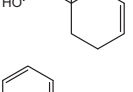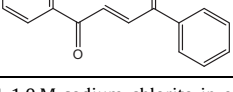
Table 2
Promotional effect of aldehydes on epoxidation of styrene with NaClO$_2$[a]

Aldehyde	Amount of aldehyde (mM)	Run time (h)	Conversion (%)	Yield of styrene oxide[b] (%)
Unpromoted	—	5	99	88
HCHO	10	4	100	88
HCHO	25	3	100	88
HCHO	50	2	96	78
Glyoxal	10	3	100	82
Glyoxal	25	2	100	87
Glyoxal	50	2	100	81
Benzaldehyde	50	3	99	85
Glucose	50	4	99	87

[a] Ethanol/water 3:1. Water is pH 7 100 mM phosphate buffer.
[b] Yields are based on GC analysis and are equal to conversion × selectivity.

Table 3
Comparison of promotional effect of HCHO in epoxidation of alkenes by sodium chlorite[a]

Substrate	Results with and without promoter[b]		
	Runtime (h)	Conv. (%)	Selectivity[c] (%)
	7	99	89
	5	99	89
	8	99	85 trans
	4	100	84 trans
	23	61	63 trans 18 cis
	23	85	72 trans 11 cis
	15	98	76
	5	96	72
	4	99	83
	2	99	44
	24	67	59
	18	98	50
	24	76	81
	18	80	78
	28	90	65
	22	95	68
	28	58	77
	22	77	85
	24	32	78
	24	65	84

[a] 1.0 M sodium chlorite in acetonitrile/ethanol/aq buffer (2:1:1, by volume) at room temperature (25 °C) and at pH ~7.
[b] For each compound, the first entry is for no promoter and the second is for 25 mM formaldehyde promoter.
[c] Yields are based on GC analysis and are equal to conversion × selectivity.

promoted reaction is accompanied by markedly reduced selectivity). Unfortunately, linear aliphatic alkenes such as 1-hexene and 5-decene are not usefully converted into the epoxide as the reactions are slow and non-selective (~20% yield with reaction times of 25 and 30 h, respectively). Similarly, selectivity in cyclohexene oxide formation was ~50%, although the cyclooctene reaction was relatively selective. Overall, the reactivity pattern indicates that this is an electrophilic oxidant system, although the electrophilic alkene *trans*-1,2-dibenzoylethylene was converted slowly into epoxide with good selectivity.
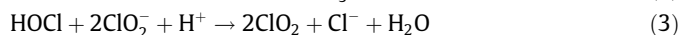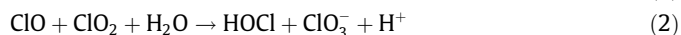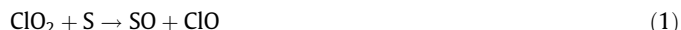
It was observed that the epoxidation of *trans*-stilbene gives *trans*-stilbene oxide alone whereas *cis*-stilbene yields *trans*-stilbene oxide as the major product. This result shows the non-stereospecificity of the reaction and is in good agreement with an earlier report on sodium chlorite epoxidations by Geng et al.[19]

We also examined pH effects in the range of 6–8 for the oxidation of styrene and found that yields of the epoxide remain >80% in that range, although at pH 8 the induction period is lengthened substantially in the absence of the promoter (to ~6 h). This long induction period at pH 8 was effectively eliminated with 25 mM formaldehyde.

The electrophilic nature of this oxidant system was further investigated by an examination of the substituent effects in styrene epoxidations (Table 4). Several *para*-substituted styrenes were investigated and compared to the results for styrene. It is observed that the rate of the reaction is in the order R = –OCH$_3$ > –CH$_3$ > –H > –Cl > –NO$_2$, which shows the electrophilicity of this epoxidation reagent. Interestingly, the overall conversion remains high given the sufficient reaction time for all substrates but the selectivities decline for the two most nucleophilic substrates (R = Me, OMe), as also observed for α-methylstyrene (Table 3).

According to Kolar and Lindgren,[17] the direct reaction of styrene with the stable free radical ClO$_2$ in the presence of chlorite yields styrene oxide via the chain reaction of Eqs. (1)–(3), where SO = styrene oxide. HOCl formed as an intermediate in

$$ClO_2 + S \rightarrow SO + ClO \qquad (1)$$
$$ClO + ClO_2 + H_2O \rightarrow HOCl + ClO_3^- + H^+ \qquad (2)$$
$$HOCl + 2ClO_2^- + H^+ \rightarrow 2ClO_2 + Cl^- + H_2O \qquad (3)$$

Eq. 2 is responsible for the formation of chlorinated byproducts via side reactions. In the presence of excess sodium chlorite, the formation of ClO$_2$ via the complex reaction of HOCl with chlorite[25] (Eq. 3) is favored over the formation of byproducts. This competition explains why styrene oxide yields increase with increasing [NaClO$_2$] (Table 1).

The loss of stereochemistry at the double bond (as illustrated by the *cis*-stilbene reaction) is consistent with a radical addition mechanism for Eq. 1 in which the intermediate (e.g., a substituted benzyl radical in the case of styrene, **1**) can undergo free rotation around the C–C bond prior to the elimination of ClO radical and closure of the epoxide ring. With radical addition as the rate determining step, substrate reactivity will tend to follow the radical stability for the addition product, thereby explaining the high reactivity of phenyl alkenes and the effect of substituents on rates (Table 4). It is notable that ClO$_2$ is isoelectronic with RO$_2^\cdot$ and intermediate **1** is analogous to that shown by Brill to account for the formation of epoxides in the autoxidation of alkenes.[26] The elimination of ClO$^\cdot$ (Eq. 1) is analogous to the elimination of RO$^\cdot$ in the autoxidation mechanism.


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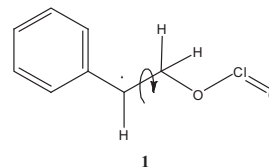
The induction period in the absence of the promoter (Fig. 1) is associated with the slow initial conversion of small amounts of chlorite to form chlorine dioxide, most likely through the reactions involving alcohol and/or the aqueous buffer. Once ClO$_2$ is produced

Table 4
Epoxidation of *para*-substituted styrenes with NaClO$_2$[a]

para-Substituent	Runtime (h)	Conversion (%)	Yield of epoxide (%)[b]
–OCH$_3$	1	100	51
–CH$_3$	3	100	60
–H	5	99	89
–Cl	6	99	78
–NO$_2$	23	96	86

[a] 1.0 M sodium chlorite in acetonitrile/ethanol/aq buffer (2:1:1, by volume) promoted by 25 mM HCHO at room temperature (25 °C) and at pH ~7.
[b] Yields are based on GC analysis and are equal to conversion × selectivity.

in sufficient amounts, the chain reaction (Eqs. (1)–(3)) becomes self-sustaining and the reaction rapidly reaches its maximum rate. To bypass the slow initiation and to improve the practicality of the reaction, direct addition of reactants that form ClO_2 via the reaction with chlorite can reduce the induction period and decrease the reaction times. It has been long known that sodium chlorite can oxidize aldehydes to their respective acids and chlorine dioxide is produced during this process.[20–22] According to Chinake et al.[20] the overall stoichiometry for chlorite oxidation of formaldehyde to formic acid is given by Eq. 4,

$$3ClO_2^- + HCHO + 2H^+ \rightarrow HCOOH + 2ClO_2 + Cl^- + H_2O \quad (4)$$
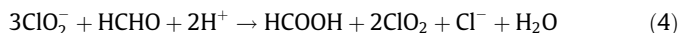
and in the presence of excess chlorite, formic acid is further oxidized to CO_2 in a second net reaction (Eq. 5).

$$3ClO_2^- + HCOOH + 2H^+ \rightarrow CO_2 + 2ClO_2 + Cl^- + 2H_2O \quad (5)$$
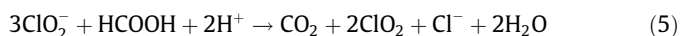
Under our aldehyde-promoted conditions,[30] ClO_2 is formed rapidly by reactions analogous to Eq. 4 with reactive aldehydes (plus Eq. 5 in the case of formaldehyde) and the chain reaction that produces epoxide is initiated without a significant induction period (Fig. 1). The promotion reaction need not achieve the stoichiometric limits in Eqs. 4 and 5 to be effective.

Acknowledgments

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30. All alkenes and reagents were purchased from commercial suppliers and used without further purification. Technical grade sodium chlorite (80%) was purchased from Fisher Scientific and recrystallized as described previously.[27] The purity of sodium chlorite was determined by the ion chromatography (Model ICS-1500, Dionex Corporation, CA, USA). General procedures for epoxidations and product analysis. A 50 mL of round-bottomed flask was charged with a solvent mixture (10 mL acetonitrile, 5 mL ethanol and 5 mL water (pH 7, 100 mM phosphate buffer) for reactions listed in Table 3). To this solvent mixture 100 mM of alkene and 50 mM of naphthalene (when used as a GC standard) were added and stirring was continued for 1 h to dissolve the alkene completely. To this mixture recrystallized sodium chlorite was added to give a 1 M solution. The reaction starts as soon as the sodium chlorite was added. The solution turned from colorless to yellow during the reaction. Product analysis was done at regular intervals. A 250 µL aliquot of the reaction mixture was quenched by 1 mL saturated aqueous solution of $Na_2S_2O_3$ and the mixture was then extracted with CH_2Cl_2 three times. The combined organic layer was washed with water and brine one time each, dried over anhydrous Na_2SO_4, and analyzed by Varian Model CP-3800 gas chromatograph equipped with a flame ionization detector (FID) using a DB MS 35 capillary column. Reaction products were identified by GC–MS when required and compared with authentic samples. Aqueous solutions of chlorine dioxide were produced by the reaction of acetic anhydride and sodium chlorite in a three tower gas train as described in the literature.[28,29] Caution: chlorine dioxide gas is explosive at higher concentrations; observe all precautions. Chlorine dioxide concentrations were obtained by UV–vis spectrophotometry, generally using the maximum at 359 nm ($\varepsilon = 1250$ M^{-1} cm^{-1}). Purity was assessed by using ion chromatography.