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Oxidative Ritter-type Chloroamidation of Alkenes Using NaCl and Oxone

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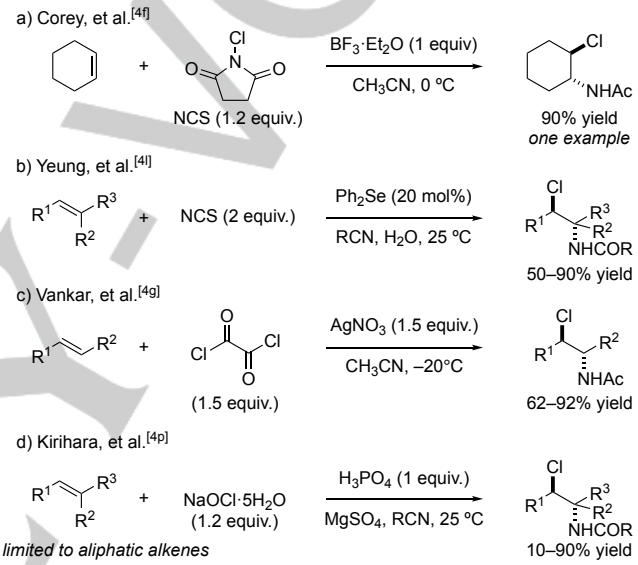
Abstract: We report a practical and environmentally benign method for the oxidative Ritter-type chloroamidation of alkenes using sodium chloride and oxone as a chlorinating source and an oxidant, respectively, in acetonitrile under mild conditions. The reaction proceeded smoothly under non-aqueous conditions without the use of any catalyst. Excellent chemoselectivity (i.e., chloroamidation versus dichlorination) could be achieved for electron-deficient styrenes. In addition, this protocol could be easily applied to 7-gram-scale synthesis.

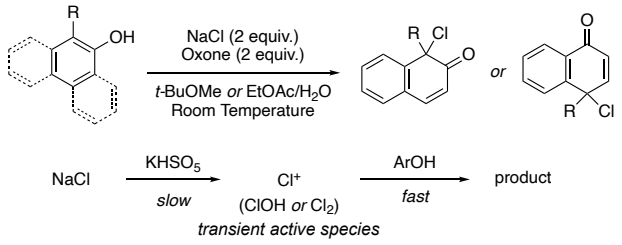
Vicinal haloamides are used as versatile building blocks for the synthesis of various natural products and biologically active compounds.[1,2] Generally, these compounds are synthesized by the haloamidation of alkene feedstocks using electrophilic halogenation reagents. To date, many elegant strategies for olefin haloamidation have been developed using transition-metal catalysts or organocatalysts.[3] Among these strategies, the Ritter-type chloroamidation of alkenes using nitriles as a solvent and nucleophile is one of the most straightforward routes to these compounds (Scheme 1).[4] For example, the groups of Corey and Yeung independently reported the Ritter-type chloroamidation of alkenes mediated by a Lewis acid or Lewis base, respectively (Schemes 1a and 1b).[4f,l] However, *N*-chlorosuccinimide (NCS) is used as an organic electrophilic chlorinating reagent, in which succinimide is generated as organic waste. On the other hand, Vankar and colleagues used oxalyl chloride as a chlorinating reagent, albeit the use of a stoichiometric amount of silver salt is required for the reaction to proceed (Scheme 1c).[4g] Very recently, Kirihara and colleagues reported the Ritter-type chloroamidation of alkenes using sodium hypochlorite pentahydrate ($NaOCl•5H_2O$)[5] as an inexpensive inorganic chlorinating reagent in the presence of phosphoric acid in nitrile solvents (Scheme 1d).[4p] However, the substrate scope is limited to aliphatic alkenes, and the reactions of vinylarenes give a complex mixture.



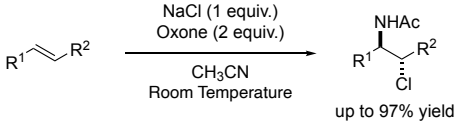
Scheme 1. Previous representative examples for Ritter-type chloroamidation of alkenes.

Recently, we reported a practical oxidative dearomative chlorination of arenols using sodium chloride and oxone ($KHSO_5•0.5KHSO_4•0.5K_2SO_4$) as a chlorinating reagent and an oxidant, respectively (Scheme 2a).[6,7] Chlorine (Cl_2) or hypochlorous acid (ClOH) might be generated *in situ* as an active electrophilic chlorinating species under acidic conditions. Most importantly, thanks to the slow generation and rapid consumption of these transient active species, the concentration of the highly reactive chlorinating species could be minimized to induce high chemoselectivity compared to stoichiometric chlorinating reagents such as sodium hypochlorite pentahydrate. Here, we applied a NaCl/oxone system to the oxidative Ritter-type chloroamidation of alkenes (Scheme 2b). The oxidative chloroamidation of various substituted styrenes proceeded in nitrile solvents under mild conditions to give the corresponding vicinal chloroamides in good to high yield. Notably, excellent chemoselectivity (i.e., chloroamidation versus dichlorination) was achieved for the electron-withdrawing group-substituted styrenes under non-aqueous conditions. Aliphatic alkenes could also be used as substrates to give the corresponding chloroamides in moderate to good yield.

a) Our previous work: Oxidative chlorinative dearomatization of arenols[6]



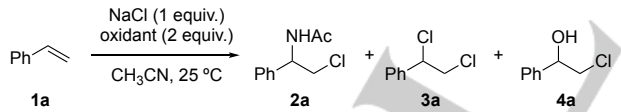
b) This work: Oxidative Ritter-type chloroamidation of alkenes



Scheme 2. Oxidative dearomative chlorination and Ritter-type chloroamidation using a NaCl/oxone system.

We commenced our study by examining the oxidative chloroamidation of styrene (**1a**) (Table 1). First, following our previous report,[6] we used 1 equivalent of NaCl and 2 equivalents of oxone in a mixed solvent of acetonitrile and water at 25 ºC. However, desired chloroamide **2a** was not obtained, and chlorohydrin **4a** was isolated as a major product along with a small amount of dichlorination side product **3a** (entry 1). To our delight, the generation of chlorohydrin **4a** was suppressed entirely in nonaqueous acetonitrile, and desired **2a** was obtained in 68% isolated yield (entry 2). However, the dichlorination pathway remained as a side reaction. A brief screening of oxidants revealed that while almost no reaction proceeded with the use of hydrogen peroxide or alkyl hydroperoxides (TBHP and CHP) (entries 3–5), the use of *meta*-chloroperbenzoic acid (*m*-CPBA) gave a complex mixture of **2a**, **3a**, **4a** and several unidentified by-products (entry 6).

Table 1. Oxidative Ritter-type chloroamidation of **1a**.[a]

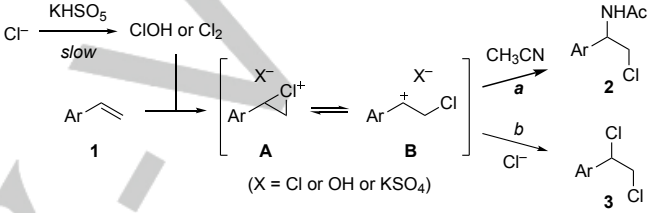


1a **2a** **3a** **4a**

Entry	Oxidant	Time [h]	Yield [%][b]		
			2a	**3a**	**4a**
1[c]	Oxone	3	<1	10	78
2	Oxone	9	70 (68)[d]	13	<1
3[e]	H_2O_2	24	<1	<1	<1
4[e]	TBHP	24	<1	<1	<1
5[e]	CHP	24	<1	<1	<1
6[f]	*m*-CPBA	1	13	4	7

[a] A solution of **1a** (0.5 mmol), NaCl (1 equiv.) and oxidant (2 equiv.) in CH_3CN (0.2 *M*) was stirred at 25 °C. For details, see the Supporting Information. [b] Determined by ^1H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. [c] A CH_3CN/H_2O (1:1) mixed solvent was used. [d] Isolated yield. [e] Unreacted **1a** was recovered (>95%). [f] Several unidentified by-products were also observed.

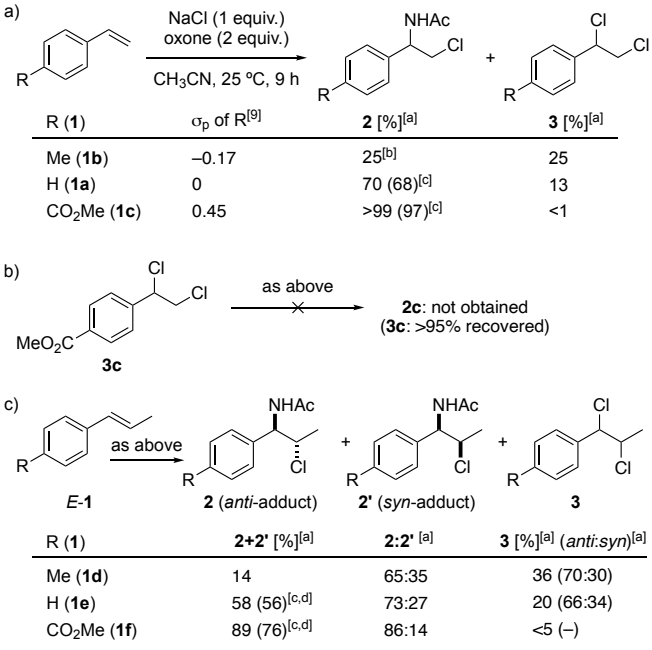
A proposed reaction mechanism is briefly summarized in Scheme 3. First, chloride ion should be oxidized by oxone to ClOH or Cl_2.[6,7] These active species might react with vinylarene **1** to produce cyclic chloriranium ion intermediate **A**, which might exist in equilibrium with linear benzylic ion intermediate **B**. These intermediates **A** and/or **B** might react with the solvent acetonitrile (*path a*) to give desired chloramide **2** after hydrolysis of the nitrilium ion. On the other hand, because of the slow generation of Cl^+ active species under non-aqueous conditions that solid reagents could not be dissolved, chloride anion in the reaction mixture might competitively react with intermediates **A** and/or **B** to afford undesired dichloride **3** (*path b*). Dichloride **3** might also be obtained by the ion-pair collapse of these intermediates (when X = Cl).[8]



Scheme 3. Proposed mechanism.

To understand the origins of the chemoselectivity between the chloroamidation and dichlorination pathways, we first investigated the substituent effect of styrenes such as 4-methylstyrene (**1b**) and methyl 4-vinylbenzoate (**1c**) as electron-rich and electron-deficient substrates, respectively, and compared them to those of **1a** (Scheme 4a). The reaction of **1b** gave an equimolar mixture of chloroamide **2b** and dichloride **3b** along with several unidentified side products. In sharp contrast, electron-deficient styrene **1c** gave the corresponding chloroamide **2c** quantitatively after a clean reaction. Concisely, the lower the electron-donating ability of the substituent (i.e., the higher σ_p[9]), the higher the chemoselectivity of the chloroamidation pathway. The possible generation of **2c** from dichloride **3c** could be excluded by a control experiment using **3c** as a substrate under identical conditions (Scheme 4b). While benzylic cation intermediate **B** would be stabilized by electron-donating substituents, electron-withdrawing substituents would destabilize intermediate **B**, and chloriranium ion intermediate **A** would be favored.[10] Therefore, the results in Scheme 4a might suggest that acetonitrile tends to react with chloriranium ion intermediate **A**, and chloride ion tends to react with benzyl cation intermediate **B** under our conditions. We next investigated the stereoselectivity of the chloroamidation reaction using *trans*-β-methyl styrenes (*E*)-**1d**–**f** as substrates under optimized conditions (Scheme 4c). As a result, a mixture of *anti*-(**2**) and *syn*-adducts (**2'**) was observed in all cases, probably due to the equilibrium between the cyclic and linear intermediates **A** and **B**.[11,12] Nevertheless, the diastereoselectivity of **2d**–**f** as well as the chemoselectivity of the chloroamidation pathway increased as the electron-donating nature of the substituents decreased, which was consistent with the substituent effect of styrenes **1a**–**c** described above. In addition, in contrast to chloroamide **2e** diastereoselectivity of dichloride **3e** was not improved compared to that of **3d**, but rather decreased slightly, suggesting that

dichlorination pathway tends to proceed via intermediate **B**, consistent with the substituent effect of styrenes **1a**–**c** described above.

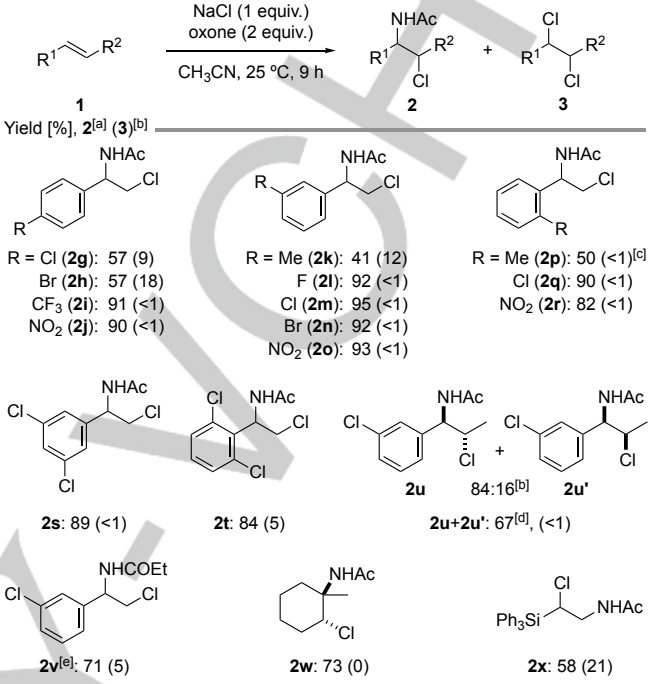


R (**1**)	σ_p of R[9]	**2** [%][a]	**3** [%][a]
Me (**1b**)	–0.17	25[b]	25
H (**1a**)	0	70 (68)[c]	13
CO_2Me (**1c**)	0.45	>99 (97)[c]	<1

R (**1**)	**2+2'** [%][a]	**2:2'** [a]	**3** [%][a] (*anti*:*syn*)[a]
Me (**1d**)	14	65:35	36 (70:30)
H (**1e**)	58 (56)[c,d]	73:27	20 (66:34)
CO_2Me (**1f**)	89 (76)[c,d]	86:14	<5 (–)

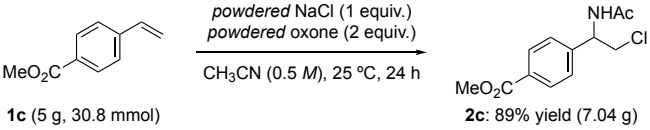
Scheme 4. Control experiments and stereoselective chloroamidation of *trans*-β-methylstyrenes **1d**–**f**. [a] Determined by ^{1}H NMR analysis. [b] Several unidentified by-products were also observed. [c] Isolated yield. [d] Isolated as an inseparable mixture of **2** and **2**'. For details, see the Supporting Information.

A series of vinylarenes **1** were examined for the oxidative chloroamidation reaction under optimized conditions (Scheme 5). As expected from the results discussed above, the chemoselective reaction of vinylarenes bearing electron-withdrawing groups such as CF_3 (**1i**) and NO_2 (**1j**, **1o**, and **1r**) at either the *ortho*-, *meta*- or *para*-positions and halogens (**1l**–**n**) at the *meta*-position proceeded to give the corresponding chloroamides **2** in high to excellent yields. On the other hand, while *ortho*-chloro-substituted **1q** gave chloroamide **2q** exclusively in 90% yield, *para*-halogen-substituted **1g** and **1h** gave the corresponding chloroamides **2** in moderate yield along with dichlorides **3** as side-products. Although the differences of these *ortho*- and *para*-substitution effects of halogens are not yet fully understood, we speculated that the linear intermediate **B** towards dichlorides might be less-stable for *ortho*-chloro-substituted styrene **1q** due to "*ortho*-effect".[13,14] In addition, dichloro-substituted styrenes **1s** and **1t** afforded the corresponding chloroamides in good yield. However, the chemoselectivity and the chemical yield of chloroamides decreased for the reactions of *meta*- and *ortho*-methyl-substituted styrenes **1k** and **1p** as in that of **1b**. The reaction of 3-chloro-β-methylstyrene ((*E*)-**1u**) gave a mixture of *anti*/*syn*-adducts **2u** and **2u'** in 67% yield (d.r. 84:16). Propionitrile could also be used as a solvent to give propanamide **2v**, albeit in a lower yield than that of acetamide **2m**. Aliphatic alkenes were also applicable under the present oxidative conditions. For example, a chemoselective oxidative chloroamidation of 1-methylcyclohexene (**1w**) proceeded to give α-tertiary amide **2v** in good yield with *anti*-selectivity.[4l] In addition, vinyltriphenylsilane (**1x**) afforded chloroamide **2x** in moderate yield along with dichloride **3x**. In this reaction, both the *anti*-Markovnikov addition to **2x** and the generation of dichlorides **3x** might be attributed to the β-silicon effect.[15]



Scheme 5. Oxidative chloroamidation of alkenes **1**. A solution of **1** (0.5 mmol), NaCl (1 equiv.), and oxone (2 equiv.) in CH_3CN (0.2 *M*) was stirred at 25 °C. [a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Although we could not detect dichloride **3p**, several unidentified by-products were observed. [d] Isolated as an inseparable mixture of **2u** and **2u'**. [e] Propionitrile was used as a solvent instead of acetonitrile. For details, see the Supporting Information.

Finally, we achieved the 60-fold scale-up of oxidative chloroamidation of **1c** (30.8 mmol) under slightly modified conditions using *powdered* NaCl and *powdered* oxone[16] under non-aqueous conditions (Scheme 6). An analytically pure chloroamide **2c** could be easily isolated in 89% yield (7.04 g) by simply washing the crude product with diethyl ether.



Scheme 6. Gram-scale oxidative chloroamidation of **1c**.

In conclusion, we have developed a practical method for the oxidative Ritter-type chloroamidation of alkenes using NaCl and oxone as a chlorinating source and an oxidant, respectively, in acetonitrile under mild conditions. The reactions proceeded smoothly under non-aqueous conditions without the use of any catalyst. Notably, excellent chemoselectivity (i.e., chloroamidation versus dichlorination) could be achieved for the electron-withdrawing group-substituted styrenes. This protocol could be easily applied to 7-gram-scale synthesis.

Acknowledgements

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Keywords: alkene • styrene • chloroamidation • oxidation • oxone

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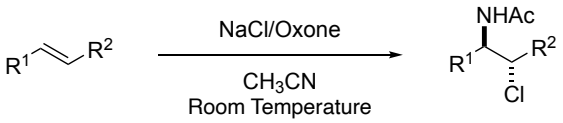

A practical and environmentally benign method for the oxidative Ritter-type chloroamidation of alkenes was developed using sodium chloride and oxone as a chlorinating source and an oxidant, respectively. The reaction proceeded smoothly under non-aqueous conditions without the use of any catalyst. Excellent chemoselectivity (i.e., chloroamidation versus dichlorination) could be achieved for electron-deficient styrenes. In addition, this protocol could be easily applied to 7-gram-scale synthesis.

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