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CHLOROAMIDATION OF ALKENES USING SODIUM HYPOCHLORITE PENTAHYDRATE AND ITS APPLICATION TO SYNTHESIS OF AZIRIDINES

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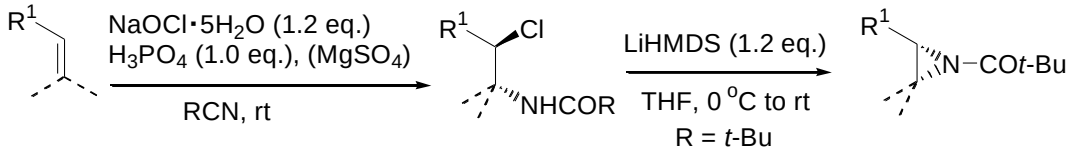
Dedicated to Professor Dr. Yasuyuki Kita on the occasion of his 77th birthday

Abstract – The reaction of alkenes with sodium hypochlorite pentahydrate ($NaOCl·5H_2O$) and phosphoric acid (H_3PO_4) in nitrile solvents resulted in a chloroamidation reaction, producing α-chloroamide derivatives in good yields without the use of a transition metal catalyst (up to 90%). *N*-Pivalazirizines were readily obtained from the resulting α-chloroamide derivatives when they were reacted with lithium hexamethyldisilazide (LiHMDS).

Haloamidation of alkenes is an attractive transformation in organic synthesis because the resulting products can be further converted to aziridines,[1] oxazolines[2] or other nitrogen containing compounds. Although it is sharp contrast to that a lot of effective methods have been developed for the halosulfonylamidation,[3] contrary to the importance, not so many methods for the haloamidation of alkenes have been reported to date.[4] During the course of developing organic synthetic reactions, using sodium hypochlorite pentahydrate ($NaOCl·5H_2O$)[5] as an eco-friendly oxidant, we observed that α-chloroamide derivatives were produced when alkenes were reacted with $NaOCl·5H_2O$ in nitrile solvents

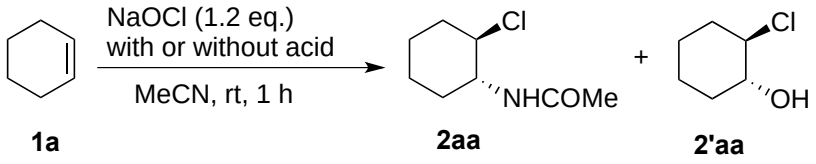
in the presence of phosphoric acid under catalyst-free conditions. The resulting chloroamides were effectively converted to aziridine derivatives (Scheme 1).



Scheme 1. Chloroamidation of alkenes using $NaOCl \cdot 5H_2O$ and H_3PO_4 in RCN (solvent) and the subsequent step forming aziridine derivatives

Initially, cyclohexene (**1a**) as a prototypical substrate was reacted with sodium hypochlorite (NaOCl) (1.2 eq.) in acetonitrile (MeCN, Table 1). The reaction of **1a** with $NaOCl \cdot 5H_2O$ in the absence of additives produced a complex mixture of compounds (run 1). We observed that when additives were used in the presence of acids such as H_3PO_4 and H_2SO_4, the desired α-chloroamide **2aa** was produced in high yields (runs 2, 3). When the substrate was reacted with the conventional aqueous NaOCl solution (13%), the side-product (chlorohydrin **2'aa**) was produced. This can be potentially ascribed to the use of an aqueous reagent (run 4).

Table 1. Optimization of reaction conditions



1a **2aa** **2'aa**

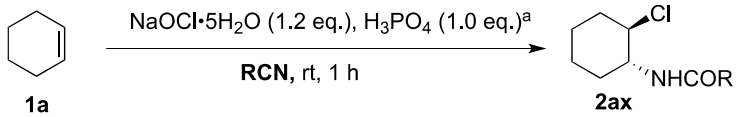
run	NaOCl	acid	yield of **2aa** (%)	yield of **2'aa** (%)
1	$NaOCl \cdot 5H_2O$	none	complex mixture	
2	$NaOCl \cdot 5H_2O$	H_3PO_4 (1.0 eq.)[a]	82[c]	not detected
3	$NaOCl \cdot 5H_2O$	H_2SO_4 (1.5 eq.)[b]	84[c]	not detected
4	13% aq. NaOCl	H_3PO_4 (1.0 eq.)	31[d]	62[d]

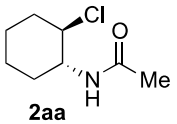
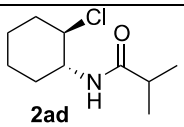
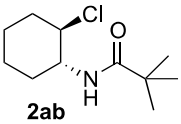
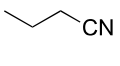
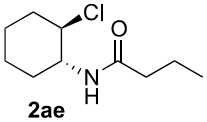
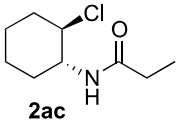
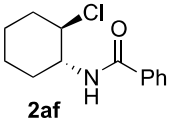
[a]100 mol% of H_3PO_4 was used (3.0 eq. as H^+). [b]150 mol% of H_2SO_4 was used (3.0 eq. as H^+). [c]Isolated yield. [d]^{1}H-NMR yield using dimethyl sulfone as internal standard.

As shown in Table 2, the reaction with the substrate **1a** was carried out in various nitrile solvents under the optimized reaction conditions (1.2 eq. of $NaOCl \cdot 5H_2O$, 1.0 eq. of H_3PO_4) and appreciable yields of

the corresponding α-chloroamides **2aa–2af** were obtained. The maximum yield of the compound **2ab** was obtained in 90% isolated yield when *t*-BuCN was used (run 2).[6]

Table 2. Reactions in various nitriles



run	RCN	product	yield (%)[b]	run	RCN	product	yield (%)[b]
1	Me−CN	 **2aa**	82	4		 **2ad**	64
2		 **2ab**	90	5		 **2ae**	62
3		 **2ac**	61	6	Ph−CN	 **2af**	84

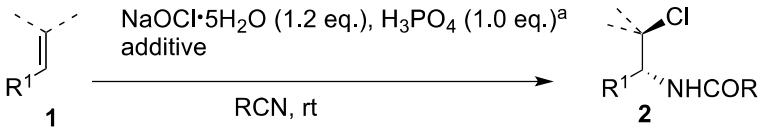
[a] 100 mol% of H_3PO_4 was used (3.0 eq. as H^+) . [b]Isolated yield.

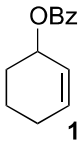
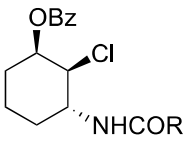
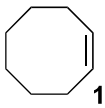
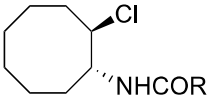
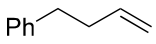
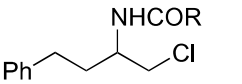
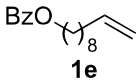
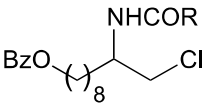
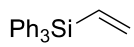
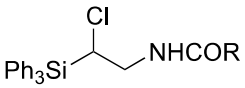
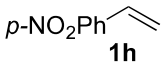
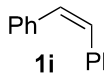
Next, various alkenes **1** were reacted with the reagents in MeCN or *t*-BuCN (Table 3).[7] The corresponding α-chloroamides were obtained when the alkenes **1b**–**1f** were used as the substrates (runs 1–11). Markovnikov-type products were obtained when the acyclic alkenes **1d–1e** were used for the reactions (runs 5–11). The vinylsilane **1f** was found to be an excellent substrate for the chloroamidation reaction reported herein. The products **2fa–2fb** (anti-Markovnikov-type, runs 12–14) were obtained in good yields. The stabilization effect produced by the silicon atom, on the β-carbocation, is the primary cause behind the observed selectivity.[8] Unfortunately, complex mixtures were obtained when conjugated alkenes (such as styrene derivatives **1h–1i**) were used for the reactions (runs 15–17). The addition of anhydrous magnesium sulfate ($MgSO_4$) improved the yields of the products (alternative route, runs 3, 4, 6, 8, 11, and 14).

A plausible reaction mechanism is shown in Scheme 2. Hypochloric acid (HOCl) or chlorine (Cl_2), formed when $NaOCl·5H_2O$ reacted with the acids present in the reaction mixture, reacted with the alkenes to form chloronium intermediates **A**. The nucleophilic attack (with the lone pair on the nitrile nitrogen) on **A** to form the nitrilium ion intermediates **B**. Intermediate **B** was hydrolyzed in the presence of water to afford the corresponding amide when the reaction was worked up. A simultaneous competing reaction that produces chlorohydrin, occurs (nucleophilic reaction between water and **A**) when a large

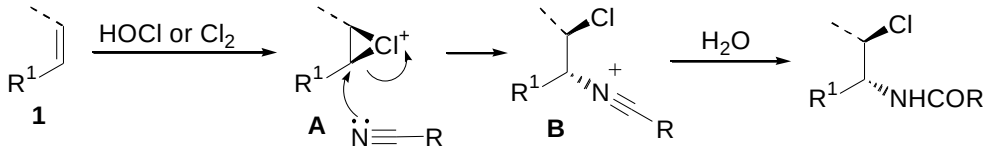
amount of water is present in the reaction mixture. Therefore, the conventional aqueous solution of NaOCl (13%) is not a suitable reagent for carrying out the chloroamidation reactions (Table 1, run 4). Anhydrous $MgSO_4$ could work as a water-absorbent and prevent the formation of chlorohydrin, resulting in improved product yields.

Table 3. Reactions with various alkenes



run	substrate	time	RCN	additive	product	yield (%)[b,c]
1	 **1b**	1 h	*t*-BuCN	-		**2bb**: 68
2	 **1c**	1 h	MeCN	-		**2ca**: 39
3			MeCN	$MgSO_4$[d]		**2ca**: 59
4			*t*-BuCN	$MgSO_4$[d]		**2cb**: 89
5	 **1d**	1 h	MeCN	-		**2da**: 58
6			MeCN	$MgSO_4$[d]		**2da**: 71
7			*t*-BuCN	-		**2db**: 16
8			*t*-BuCN	$MgSO_4$[d]		**2db**: 44
9	 **1e**	1 h	MeCN	-		**2ea**: 48
10			*t*-BuCN	-		**2eb**: 10
11			*t*-BuCN	$MgSO_4$[d]		**2eb**: 56
12	 **1f**	2 h	MeCN	-		**2fa**: 60
13		4.25 h	*t*-BuCN	-		**2fb**: 27
14		4.25 h	*t*-BuCN	$MgSO_4$[d]		**2fb**: 41
15	 **1g**	0.8 h	MeCN	-	complex mixture	
16	 **1h**	0.8 h	MeCN	-	complex mixture	
17	 **1i**	0.5 h	MeCN	-	complex mixture	

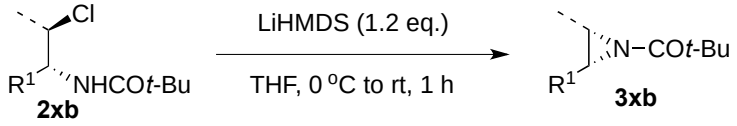
[a]100 mol% H_3PO_4 was used (3.0 eq. as H^+). [b]Isolated yield. [c]Some by-products including chlorohydrines were also produced. [d]20 eq. of $MgSO_4$ was added.

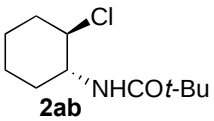
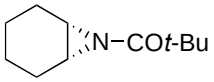
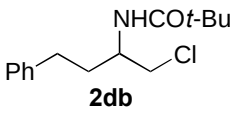
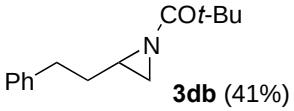
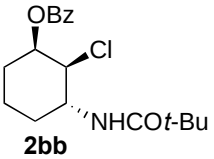
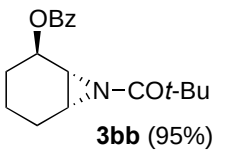
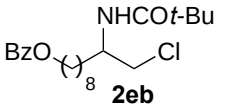
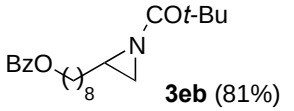
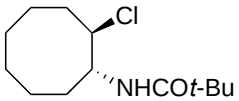
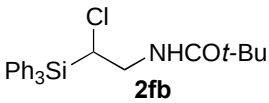
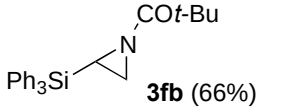


Scheme 2. Plausible reaction mechanism

Finally, to demonstrate the utility of the synthesized products, *N*-pivalaziridines **3xb** were synthesized from the corresponding α-chloropivalamides **2**. In most cases, the desired aziridines **3xb** were obtained in good yields when the reactions were carried out with **2xb** as the substrate in the presence of lithium hexamethyldisilazide (LiHMDS) (Table 4).[9,10] Curiously, **2cb** was completely inert under the reaction condition (run 3).[11] It is notable that the 2-silylated aziridine **3fb** was obtained in 66% yield.

Table 4. Formation of aziridines **3xb** from α-chloropivalamides **2xb**



run	2xb	3xb[a]	run	2xb	3xb[a]
1	 **2ab**	 **3ab** (99%)	4	 **2db**	 **3db** (41%)
2	 **2bb**	 **3bb** (95%)	5	 **2eb**	 **3eb** (81%)
3	 **2cb**	no reaction	6	 **2fb**	 **3fb** (66%)

[a] Isolated yield.

In conclusion, we observed that the reaction of cyclic and acyclic alkenes with $NaOCl·5H_2O$ (1.2 eq.) and H_3PO_4 [1.0 eq. (3.0 eq. as H^+)] in nitrile solvents produced the corresponding α-chloroamides. The addition of anhydrous $MgSO_4$ could improve the yields of the α-chloroamide derivatives. *N*-Pivalaziridines **3** were obtained in excellent yields (maximum yield: 99%) from the reaction of α-chloropivalamides **2xb** with LiHMDS (1.2 eq.) in THF. The facile synthetic protocol was established using commercially available reagents ($NaOCl·5H_2O$, *t*-BuCN, H_3PO_4, and LiHMDS). Currently, these

reactions and application to synthesis of other nitrogen containing compounds (e.g. oxazolines) are being investigated in detail, and the results will be published in a “full paper” in the near future.

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

Supplementary (melting point, ^1H and ^{13}C NMR, IR, ESI-HRMS) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27100/103/2

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6. Representative procedure for the reaction of cyclohexene in various RCN: Cyclohexene (82 mg, 1.0 mmol) was resolved in nitrile (5 mL), and the mixture was stirred and cooled to 0 °C. H_3PO_4 (58 μL, 1.0 mmol) was added to the mixture, and then $NaOCl{\cdot}5H_2O$ (197 mg, 1.20 mmol) was slowly added. The resulting mixture was stirred and warmed to room temperature for 1 h. Saturated aqueous sodium hydrogensulfite (sat. aq. $NaHSO_3$) (10 mL) was added to the reaction mixture. The resulting mixture was extracted with EtOAc (30 mL × 3), the extract was washed with brine (30 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by silica-gel column chromatography (using hexane-EtOAc as an eluent) to obtain the pure sample of α-chloroamide.
7. Representative procedure for the chloroamidation of alkenes: Alkene (1.0 mmol) was resolved in MeCN or *t*-BuCN (5 mL), and the mixture was stirred and cooled to 0 °C. H_3PO_4 (58 μL, 1.0 mmol) and [$MgSO_4$ (2.4 g, 20 mmol)] were added to the mixture, and then $NaOCl{\cdot}5H_2O$ (197 mg, 1.20 mmol) was slowly added. The resulting mixture was stirred and warmed to room temperature for 1 h. Saturated aqueous sodium hydrogensulfite (sat. aq. $NaHSO_3$) (10 mL) was added to the reaction mixture. The resulting mixture was extracted with EtOAc (30 mL × 3), the extract was washed with brine (30 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was purified by silica-gel column chromatography (using hexane-EtOAc as an eluent) to obtain the pure sample of α-chloroamide.
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9. Representative procedure for the aziridine formation from α-chloropivalamides **2**: Chloropivalamide **2** (0.1 mmol) was resolved in anhydrous THF (2 mL), and the mixture was stirred and cooled to 0 °C. Lithium hexamethyldisilazide (1.0 M in THF, 0.12 mL, 0.12 mmol) was added at once, and the

reaction mixture was stirred for 1 h. The reaction was quenched with pH 7 buffer solution (potassium phosphate monobasic sodium hydroxide, 0.2 mL). The reaction mixture was extracted with Et_2O (5 mL × 3), and the extract was washed with brine (20 mL), dried over $MgSO_4$, and filtered. The filtrate was evaporated, and the residue was purified by silica-gel column chromatography (using hexane-EtOAc as an eluent) to obtain the pure sample of *N*-pivalaziridines **3**.

10. Corey et al. reported that the reaction of bromoamides with 1.2 eq. of LHMDS in THF at 0 °C afforded the corresponding *N*-acylaziridines.[4a] They also reported that the exposure of bromoamides to 2.0 eq. of Et_3N and 0.2 eq. of DBU in DME at reflux provided the corresponding oxazolines.[4a]
11. The chloropivalamide **2cb** was unreacted even in the reaction with LiHMDS (2.4 eq.) in THF under reflux conditions. The reason why **2cb** is inactive for this reaction is currently unclear. We estimate that **2cb** can not adopt suitable conformations required for the aziridine formation. Research to elucidate the reason is currently underway.