The Halogenation of Aliphatic C–H Bonds with Peracetic Acid and Halide Salts

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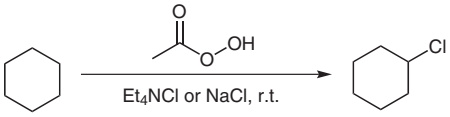
Abstract: Hydrocarbons react with molar concentrations of peracetic acid and halide salts to yield predominantly monohalogenated products under optimum conditions, with chlorination being more oxidatively efficient than bromination. The alkane halogenation proceeds at ambient temperature and does not require a heavy-metal catalyst. The observed reactivity is consistent with a radical mechanism, in which the peracid initially reacts with the halide ions to yield halogen-atom radicals, which ultimately oxidize the hydrocarbon. Although the reactivity proceeds slightly more efficiently in acetonitrile, the halogenation protocol works well in water.

Key words: alkanes, oxidation, halogenation, free radicals, green chemistry

The direct conversion of aliphatic C–H bonds to more useful functional groups is a topic of intense research.[1–4] Compounds containing C–X bonds (X = Cl, Br), in particular, are synthetically versatile and represent valuable precursors to more complex organic products due to their roles in C–C coupling reactions.[5–9] Additionally, many natural products of pharmaceutical interest contain C–Cl and C–Br functionalities; examples with antitumor activity include certain monoterpene derivatives and nostocyclophanes.[10] The installation of a halogen atom can improve an organic molecule's capability to enter cells and/or greatly impact the interaction with its biological target,[11] and the halogen functional groups may be essential for the documented medicinal benefits of these natural products.

Much progress has been made recently towards the halogenation of aromatic C–H bonds, particularly with respect to finding more environmentally benign terminal oxidants for the reactivity.[12–18] Less advancement has been made in the development of mild reactions capable of halogenating aliphatic C–H bonds.[9,12,19] The procedure used most commonly in industry is free-radical halogenation, in which either Cl_2 or Br_2 serve as both terminal oxidant and halogen source. The severe reactivity of Cl_2 and Br_2 complicates their use as reagents. For chlorination, iodobenzene dichloride ($PhICl_2$) sometimes serves as an alternative.[15,20,21] Upon irradiation, $PhICl_2$ can chlorinate cyclohexane and toluene.[20] One attractive benefit of $PhICl_2$ is that it can be prepared from ionic chloride sources; however, it is unstable to light and heat and readily decomposes during storage.[22] Furthermore, the analogous bromination with iodobenzene dibromide has not been reported. The transition-metal complex $[Fe^{II}(TPA)Cl_2]$ (TPA = tripicolylamine) uses *tert*-butylhydroperoxide (TBHP) as a terminal oxidant to convert cyclohexane to chlorocyclohexane.[23,24] The chloride can be replaced by bromide, resulting in bromination.[23,24] The iron-mediated halogenation chemistry is stoichiometric with respect to the metal complex; adding further equivalents of TBHP leads to substrate oxygenation instead of halogenation.[23]



Scheme 1

Reported here is a novel synthetic protocol capable of converting nonactivated aliphatic C–H bonds to C–Cl and C–Br functional groups. A mixture of peracetic acid (PA) and a halide salt oxidizes cyclohexane to chloro- or bromocyclohexane selectively, with only traces of higher-order halogenation products observed under optimum conditions (Scheme 1). A previously reported method uses *meta*-chloroperbenzoic acid (MCPBA) to perform the same transformation at a lower yield.[19] Our process has four benefits over most previously reported halogenation reactions.[9,25–27] First, PA is a relatively innocuous terminal oxidant, particularly compared to the more commonly used Cl_2 and Br_2.[9,27] Second, the halogen source is a halide salt, as opposed to an elemental halogen or a halogenated solvent, such as chloroform or carbon tetrachloride.[25] Third, the reported halogenation requires neither high temperatures nor a heavy-metal catalyst to proceed.[26] Fourth, the PA-mediated halogenation can be adapted to work in water. Despite the relatively mild conditions, the reaction can activate strong aliphatic C–H groups, such as the 95–100 kcal mol^{-1} bonds found in cyclohexane.[28]

When treated with high concentrations of tetraethylammonium chloride (TEACl) and PA in acetonitrile (MeCN), cyclohexane is converted into predominantly chlorocyclohexane, with traces of cyclohexanone and negligible amounts of higher-order chlorinated products when the substrate is present in excess of the oxidant (Table 1, Figure 1). When the concentration of oxidant exceeds that of the substrate, polychlorinated products do

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form (Table 2). With 1.32 M TEACl and 0.132 M PA, the oxidative efficiency of the chlorination is 72% (Table 1, entry 5); the other terminal oxidants that were investigated do not promote halogenation as efficiently. Reactions with TBHP, H_2O_2, and iodosobenzene yield, at best, trace quantities of chlorocyclohexane, as assessed by GC analysis of the reaction mixtures. With 1.32 M TEACl and 0.132 M of the peracid MCPBA, the oxidative efficiency is only 21% (Table 1, entry 4), consistent with the results reported by Kojima et al.[19]

Table 1 Reactivity of Cyclohexane[a]

Entry	Oxidant	Halide salt	Halide [M]	Efficiency (%)[b]	X/O ratio
1	H_2O_2	Et_4NCl	1.32	<1	–[c]
2	*t*-BuO_2H	Et_4NCl	1.32	<1	–[c]
3	PhIO	Et_4NCl	1.32	1.3	0.08
4	MCPBA	Et_4NCl	1.32	21	4.8
5	PA	Et_4NCl	1.32	72	71
6[d]	PA	Et_4NBr	0.66	30	93
7[e]	PA	NaCl	1.32	36	16
8[e]	PA	NaCl	6.00	59[f]	56
9[e]	PA	NaBr	3.33	16	–[g]
10	PA	Et_4NCl	0	0	–[g]
11	PA	Et_4NCl	0.132	56	4.1
12	PA	Et_4NCl	0.266	58	5.7
13	PA	Et_4NCl	0.667	62	11
14	PA	Et_4NCl	1.32	72	71
15	PA	Et_4NCl	1.98	63	114
16	PA	Et_4NCl	2.64	40	109

[a] Standard reaction conditions: 1.32 M cyclohexane, 0.132 M oxidant, 1.8 mL total volume, 22 °C, 8 h.
[b] Efficiency defined as percent yield based on the oxidant.
[c] Trace amounts of cyclohexanol, cyclohexanone, and chlorocyclohexane are present.
[d] Concentration of oxidant is 0.264 M.
[e] Water used as solvent. The pH during the reaction is 4.
[f] An isolated yield of 28% is reported in the Supporting Information.
[g] No oxygenated products observed.

The oxidative efficiency of the reaction depends on the identity and concentration of the halide salt (Figure 1). When no TEACl or tetraethylammonium bromide (TEABr) is present, no oxidation occurs. The efficiency increases with the concentration of TEACl until it reaches 10 equivalents relative to the oxidant. Above this ratio, the yield of chlorocyclohexane decreases. The incidence of cyclohexanone, the oxygenated byproduct, steadily decreases with increasing halide concentration. With 1 equivalent of chloride relative to oxidant, roughly 20% of the PA oxidizes cyclohexane to cyclohexanone instead of the chlorinated product. At higher concentrations of chloride, this oxygenated byproduct accounts for less than 1% of the oxidized cyclohexane. Unlike the MCPBA-mediated halogenation reported by Kojima et al.,[19] PA-promoted chlorination is much more efficient than the analogous bromination. The PA-promoted bromination uses TEABr as the halide source and has an optimum efficiency of just 30%. The bromination reactions, however, generally yield less of the ketone byproduct.

The reaction also proceeds in water, albeit less efficiently. The peak efficiencies are 59% for chlorination and 16% for bromination (Table 1). The reduced oxidative efficiency likely results from the immiscibility of the cyclohexane substrate and water. There is precedence for aqueous halogenation reactions; a system involving H_2O_2 and HBr was reported to brominate benzylic C–H bonds.[12,29] As with the protocol reported in this manuscript, the halogenation chemistry of the H_2O_2–HBr system proceeds at room temperature and does not require a metal catalyst. However, neither the reactivity of the H_2O_2–HBr mixture with more oxidatively robust alkanes nor attempts at chlorination were reported.[29]

Anthracene, toluene, cyclohexene, and adamantane were tested as alternate substrates for the chlorination reaction in order to assess its regioselectivity and its tolerance for olefins and aromatic C–H bonds (Table 2). Anthracene is halogenated to a mixture of mono- and polychlorinated products, demonstrating a second mode of reactivity. Under the reaction conditions, acetyl hypochlorite could potentially form and provide Cl^+ for electrophilic aromatic substitution reactions.[30–32] Since toluene contains both benzylic and aromatic C–H bonds, it was selected as a substrate in order to assess the relative speeds of the aliphatic and aromatic C–H halogenations. The products of toluene chlorination are mostly chloromethylbenzenes, and benzyl chloride accounts for only 5% of the oxidized products (Table 2). The product distribution demonstrates that the aromatic C–H halogenation proceeds more rapidly than the aliphatic C–H oxidation. The investigation of the aromatic C–H oxidation is ongoing in our laboratory.

Cyclohexene is oxidized to *trans*-1,2-dichlorocyclohexane with TEACl as the halide source and *trans*-1,2-dibromocyclohexane with TEABr as the halide source (Table 2). The bromination reaction proceeds much more cleanly than the chlorination, which yields several side products, many of which are not readily identifiable. The dihalogenated major products have previously been observed in the oxidation of cyclohexene by Cl_2 and Br_2. Adamantane is oxidized to a mixture of 1- and 2-chloroadamantanes with a preference for the activation of the C–H bonds on the tertiary carbons (Table 2). The observed lack of regioselectivity for the chlorination of adamantane is suggestive of a radical mechanism.

The color changes that accompany the halogenation reactions are consistent with the presence Cl_2 and Br_2 in the reactive mixture. During the chlorination reactions, the

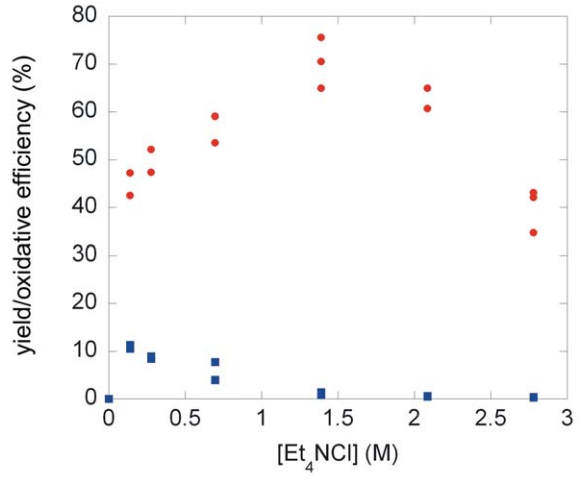
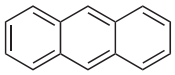
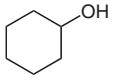


Figure 1 Dependence of the oxidative efficiencies for the formation of chlorocyclohexane (red) and cyclohexanone (blue) on the concentration of chloride, added in the form of TEACl. The starting concentration of cyclohexane was 1.32 M, whereas the starting concentration of peracetic acid was 0.132 M.

Table 2 Reactivity of Other Hydrocarbon Substrates[a]

Substrate	Efficiency (%)	Identified products
	100	9,10-dichloranthracene (77%), anthroquinone (19%), 9,10-tetrachloro-9,10-dihydroanthracene (4%)
	24[b]	1-chloroadamantane (79%), 2-chloroadamantane (21%)
	46	chloromethylbenzenes (94%), benzyl chloride (6%)
	100	cyclohexanone (100%)
	44	chlorocyclohexane (72%), cyclohexanone (7%)[d]
	100	1,2-dichlorocyclohexane (21%), 3-chlorocyclohexene (<1%)
	100[c]	1,2-dibromocyclohexane (77%), 3-bromocyclohexene (23%)

[a] Standard reaction conditions: 0.050 M substrate, 0.50 M TEACl, 0.20 M PA in 10 mL MeCN, 22 °C, 8 h.
[b] CH_2Cl_2 used instead of MeCN. An isolated yield of 20% is reported in the Supporting Information.
[c] 0.5 M TEABr used instead of TEACl.
[d] Dichlorocyclohexanes account for the remainder of the product.

solution turns faint green before fading to pale yellow; this color completely disappears when the reaction is put under reduced pressure, consistent with the loss of dissolved chlorine gas. During bromination, the solution turns brownish orange, suggesting the presence of Br_2. Kojima et al. observed similar spectral features in the previously reported halogenation reactions with MCPBA.[19]

The observation of Cl_2 and Br_2 is intriguing since the reactions occur at room temperature and without a heavy-metal catalyst. In the absence of hydrocarbon substrates, this may represent an alternative to the Deacon process, which uses high temperatures and a copper catalyst to produce Cl_2 from chloride salts and dioxygen.[33]

Although most halogenation reactions were run under ambient light, the chlorination of cyclohexane was also found to proceed in the dark. During these latter reactions, the solutions still turn green, suggesting that the reaction between PA and the chloride salt is not initiated by photons. The oxidative efficiencies of the reactions run in the dark are identical within error to those of reactions run under ambient light.

One mechanistic possibility for the alkane oxidation is that the peracid may initially convert the alkane to an alcohol, which would then undergo acid-catalyzed nucleophilic substitution to form the organohalide product. Under the conditions used to convert cyclohexane to chlorocyclohexane, cyclohexanol was converted into cyclohexanone exclusively (Table 2). Additionally, the alcohol was stable in a solution of acetic acid and TEACl at the temperature and duration used for the experiments, providing further evidence that cyclohexanol is not a plausible intermediate for these reactions and that cyclohexane is oxidized directly to chlorocyclohexane.

The lack of regioselectivity in the adamantane reactions and the production of elemental halogens suggest the intermediacy of halogen atom radicals. Based on the reduction potentials of the species involved, peracetic acid ($E^0 = 2.05$ V vs. NHE)[34] is thermodynamically capable of oxidizing Cl^- (Cl_2, $E^0 = 1.36$ V vs. NHE) and Br^- (Br_2, $E^0 = 1.07$ V vs. NHE) to chlorine and bromine radicals, respectively.[35] The PA is converted into acetate and water during this process. The halogen-atom radicals are believed to be responsible for the abstraction of the hydrogen atom from the alkane. Similar chemistry was proposed for the oxidation of enones and alkenes with oxone and sodium halides, although no aliphatic C–H activation was reported.[36] When chlorination of cyclohexane is attempted in the presence of $BrCl_3C$, bromocyclohexane is observed as a side product, consistent with the intermediacy of a cyclohexyl radical.

The reliance of the halogenation chemistry on the initially generated halogen atom radicals may explain the nonlinear dependence of the oxidative efficiency on the halide concentration. We hypothesize that at higher concentrations of chloride, the elevated production of Cl radicals facilitates the formation of Cl_2. The conversion of Cl radicals to gaseous Cl_2 removes the oxidant from the reaction mixture, thereby reducing the oxidative efficiency of alkane halogenation. The greater overpotential for the oxidation of bromide relative to chloride would hasten the production of bromine radicals relative to chloride radicals. Consequently, more of the bromide may be diverted into Br_2 production instead of alkane halogenation, ex-

plaining the lower oxidative efficiency of PA-mediated bromination relative to the analogous chlorination.

To summarize, we report a novel procedure to halogenate hydrocarbons with nonactivated aliphatic C–H bonds that uses commercially available PA as a terminal oxidant and a halide salt as the terminal halogen source. The synthetic protocol can be adapted to work in water, with NaCl or NaBr as the halogen source. The incidence of side products can be modulated and minimized by adjusting the concentrations of oxidant and halide. The major drawback to this method is that both aromatic C–H activation and the dihalogenation of alkenes proceed much more quickly than aliphatic C–H activation.

Proton and carbon[13] nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were collected on either a 400 MHz or a 250 MHz Bruker AV spectrometer. All NMR spectra were referenced to internal standards. Gas chromatography (GC) was performed on a Hewlett Packard 5890 gas chromatograph with either a flame ionization detector (FID) or a Fissons Instruments electrospray mass spectrometry detector (GC-MS). High resolution mass spectrometry (HRMS) data were acquired at the Mass Spectrometry Center at Auburn University on a Microflex LT MALDI-TOF Mass Spectrometer (Bruker Corporation).

EtOH was purchased from Fluka and used as received. NaCl, NaBr, Na_2CO_3, $MgSO_4$, pentane, CH_2Cl_2, chlorobenzene, cyclohexanol, iodosobenzene (PhIO), PA (32% in AcOH), TBHP, H_2O_2, and MCPBA were bought from Sigma-Aldrich and used without further purification. The latter five chemicals were stored in a refrigerator when not in use. Anhydrous MeCN, TEACl, TEABr, toluene, adamantane, cyclohexene, and cyclohexane were purchased from Sigma-Aldrich and stored in a nitrogen atmosphere drybox to keep them free of oxygen and moisture. Anthracene was bought from Sigma-Aldrich and recrystallized twice from EtOH prior to use. Acetonitrile-d_3 and chloroform-d ($CDCl_3$) were purchased from Cambridge Isotopes.

Each reaction was run at least three times to ensure reproducibility. The substrate and the halide salt were first put under nitrogen. After these reagents were dissolved, the oxidant was added dropwise. The system was subsequently sealed and stirred for 8 h at 22 °C. At the end of the reaction, chlorobenzene was added as an internal reference before product analysis by gas chromatography. Chlorobenzene was selected as an internal standard since it was found to be inert under the reaction conditions. Parallel reactions were run in deuterated solvents, such as MeCN-d_3, in order to confirm the identities and ratios of the products by ^{1}H NMR. This general procedure was followed for all substrate reactions except where noted otherwise. Representative reactions are discussed in greater detail in the Supporting Information.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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