Oxidation of Cycloalkanols to the Corresponding Cycloalkanones with Chlorine in the Presence of Nitroxide Radical as a Mediator

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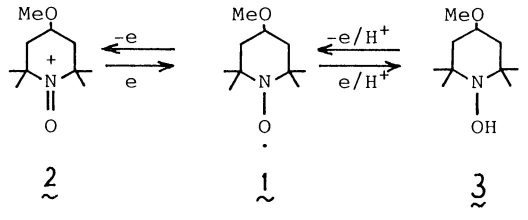
Synopsis. A method for the oxidation of cyclic alcohols to the corresponding cyclic ketones with 2,2,6,6-tetramethyl-1-piperidinyloxyl (a mediator) and chlorine is described. This oxidation involves an oxoaminium salt, formed from the nitroxide radical and chlorine, which oxidizes cyclic alcohols to give the corresponding ketones in good yields.

It is well-known that 2,2,6,6-tetramethyl-1-piperidinyloxyl[1] (nitroxide radical **1**) and its derivatives show a unique redox behavior (Scheme 1). Among these compounds **1**—**3**, oxoaminium salt **2** is widely utilized as both stoichiometric and catalytic oxidant for the oxidation of some alcohols,[2,3] amines,[4] and hydroxide ion.[5] Whereas **2** is usually prepared by chlorine or bromine oxidation of **1**,[2,5] in the catalytic reaction **2** is generated in situ from catalytic amount of **1** by the oxidation with the added oxidant such as copper(II) ion, iron(III) ion, hypobromite ion and electrode (anode).[3,4] However, neither chlorine nor bromine had been used as the apparent oxidant in these catalytic reactions mediated by **1**, probably because of the fact that chlorine (or bromine) itself is capable of oxidizing substrates. However, it should be possible to construct a new redox system using chlorine and **1** if chlorine reacts with **1** sufficiently faster than with substrate and product, and it is very likely in the case where the substrate is alcohol. On the other hand, although several suitable oxidants such as CrO_3/pyridine,[6] CrO_3/H_2SO_4[7] and dimethyl sulfide/*N*-chlorosuccinimide[8] are reported for the oxidation of cycloalkanols, each of them suffers disadvantages such as harmfulness of Cr(VI) and the cost. If a novel oxidation system consisting of a catalytic amount of **1** and chlorine as an apparent oxidant can be performed, it is of great use in the light of the simplicity of the reaction system and the cost. In this paper we describe both stoichiometric and catalytic oxidation of cycloalkanols.



Scheme 1.

Results and Discussion

Before studying on the catalytic oxidation using **1**, stoichiometric reaction with **2** was carried out, since **2** is formed in situ in the catalytic reaction with **1**. Various cycloalkanols were oxidized with 1.0 to 1.5 fold of **2** in dichloromethane at room temperature. In the cases of unsubstituted cycloalkanols the oxidation proceeded smoothly (within 10 minutes the yield reached over 80%) to yield the corresponding ketones regardless the ring-size. However, since **2** is a sterically bulky oxidant, in the cases of 2-substituted cyclohexanols the yield of ketones decreased with the increase of the bulkiness of the substituent at the 2-position of the substrate (Table 1). In addition, cis alcohol seems more reactive to **2** than trans one, though its origin remains obscure at the moment. Besides the oxidation product, hydroxylamine **3** was quantitatively obtained as the salt of hydrochloric acid. These results suggest the possibility of nitroxide radical-catalyzed oxidation of cycloalkanols with chlorine.

Then the new oxidation system containing **1** as a

Table 1. Oxidation of Cycloalkanols with Oxoaminium Chloride **2**[a]

Substrate	Configuration (Cis:Trans)	Oxidant equiv	Time min	Yield[b] %
Cyclopentanol	—	1.0	60	85 (64)
Cyclohexanol	—	1.0	60	81 (63)
Cycloheptanol	—	0.9	30	89 (79)
Cyclooctanol	—	1.0	60	89 (59)
Cyclododecanol	—	1.0	5	86 (74)
2-Methylcyclohexanol	23:76[c]	1.0	30	44
2-Cyclohexylcyclohexanol	70:30[b]	1.0	60	32[d]
(1*S*,2*S*,5*R*)-Neomenthol	100:0	1.0	60	22
dl-Menthol	0:100	1.0	60	8

a) In dichloromethane at room temperature. b) Determined by GC using an internal standard. Isolated yield in parentheses was determined in the experiment using 1.5 equivalent of **2** (100% conversion). c) Owing to supplier. d) Configuration of recovered alcohol was cis:trans=52:48.

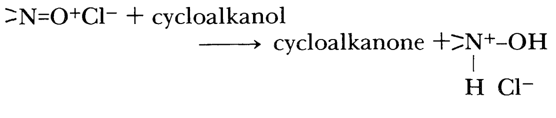
Table 2. Chlorine Oxidation of Cycloalkanols Mediated by **1**[a)]

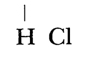
Ring size	Chlorine	**1**	Conv.[b)]	Yield[b)]	Chlorocycloalkanone[b)]	Selectivity[c)]
	equiv	mol%	%	%	%	%
6	1.0	10	76	63	2	83
6	1.4	10	100	85	2	85
6	0.8	1	21	14	1	67
6	0.8[d)]	0.5	40	28	2	71
6	1.0	0	21	12	4	56
6	1.6	0	30	16	7	55
5	1.6	10	76	64	—[e)]	84
7	1.8	10	91	76	2	83
8	1.8	10	86	74	—[e)]	85
12	1.6	10	96	80	3	84

a) In dichloromethane at room temperature. Chlorine introduction rate was 0.35 equiv h^{-1}. b) Conversion of cycloalkanol, yield of cycloalkanone, and yield of 2-chlorocycloalkanone were determined by GC using an internal standard. c) Selectivity=yield of cycloalkanone/conversion of cycloalkanol. d) Chlorine introduction rate was 0.035 equiv h^{-1}. e) Not detected.

mediator and gaseous chlorine as an apparent oxidant (actual oxidant was **2**) was constructed. All the required and possible reactions are shown in Eqs. 1—7. Equations 1 and 2 are identical with those of the stoichiometric oxidation. Because hydrochloric acid generated during the oxidation prevents the oxidation cycle[3c)] (while **3** is oxidized easily even by oxygen,[9)] probably hydroxylamine hydrochloride (**4**) is not oxidized easily to nitroxide radical), it is necessary to convert **4** to **3** by the action of base (Eq. 3). Then, chlorine oxidizes **3** to **1** while the base neutralizes hydrochloric acid (Eq. 4). The sum of Eqs. 1—4 results in chlorine oxidation of cycloalkanol to cycloalkanone (Eq. 5). On the other hand, the other reactions such as direct oxidation of cycloalkanol with Cl_2 (Eq. 6) and chlorination of generated cycloalkanone with Cl_2 (Eq. 7) may also proceed.

$$>N\text{-}O^{\cdot} + 1/2\,Cl_2 \longrightarrow >N{=}O^{+}Cl^{-} \tag{1}$$


$$>N{=}O^{+}Cl^{-} + \text{cycloalkanol} \longrightarrow \text{cycloalkanone} + \underset{\substack{|\\ H\ Cl^{-}}}{>N^{+}}\text{-}OH \tag{2}$$


$$\underset{\substack{|\\ H\ Cl}}{>N^{+}}\text{-}OH + \text{base} \longrightarrow >N\text{-}OH + \text{salt} \tag{3}$$

$$>N\text{-}OH + 1/2\ Cl_2 + \text{base} \longrightarrow >N\text{-}O^{\cdot} + \text{salt} \tag{4}$$

$$Cl_2 + \text{cycloalkanol} + 2\ \text{base} \longrightarrow \text{cycloalkanone} + 2\ \text{salt} \tag{5}$$

$$\text{cycloalkanol} + Cl_2 \longrightarrow \text{cycloalkanone} + 2\ HCl \tag{6}$$

$$\text{cycloalkanone} + Cl_2 \longrightarrow \text{chlorocycloalkanone} + HCl \tag{7}$$

Preliminarily, chlorine was introduced slowly (using microfeeder, 0.35 equiv h^{-1}) to the mixture of cyclohexanol and 10 mol% of **1** to the alcohol and Na_2CO_3 (2 equiv, powder) in dichloromethane. But within 30 min, red color of the reaction mixture owing to **1** and **2** faded out (suggesting that **1** and **2** were not regenerated) and a very small amount (below 1%) of cyclohexanone was detected. Since Eq. 3 is a heterogeneous reaction, it may be the rate-determining step of this redox cycle. We investigated some bases such as NaOH with triethylbenzylammonium chloride (as a phase-transfer catalyst) and basic alumina, and found that finely ground and ignited Na_2CO_3 was an effective base. By using finely ground Na_2CO_3, the nitroxide radical-mediated chlorine oxidation of cycloalkanol was carried out under various conditions. Results are listed in Table 2. With 10 mol% of **1** to the alcohol, the conversion of cyclohexanol reached 76% with an equivalent of Cl_2, and with 1.4 equivalent of chlorine the conversion reached 100%. Moreover, the oxidation selectivity (yield of ketone/conversion of alcohol) was over 80% even at the last stage where the concentration of cyclohexanol became low and that of cyclohexanone high. In contrast, the control experiment without **1** resulted in a low conversion of cyclohexanol and a low selectivity. With 1 mol% of **1**, both the conversion and the selectivity were unsatisfactory. In this case, the rate of the chlorine introduction seems to be too fast since an easy calculation suggests that 0.35 equiv/h roughly equals to 2 min/cycle. A ctually, slower introduction of chlorine enhanced the selectivity even with 0.5 mol% of **1** (8.5 min/cycle). In this case, the turnover number of **1** (calculated without regarding the direct oxidation of alcohol and ketone by chlorine) reached 56 turns.

As well as cyclohexanol, the other cycloalkanols were oxidized by this system in high selectivity (over 80%) under the same conditions. In all cases, little or no chlorinated cycloalkanones were detected even at the last stage of the oxidation, suggesting that the oxidation by this catalytic reaction cycle is superior to the direct oxidation by chlorine.

In conclusion, a new and simple oxidation system was established employing **1** as an effective mediator and chlorine as an apparent oxidant. This system possesses three (or more) outstanding characteristics as follows: i) High conversion and high selectivity can be attainable in this system. ii) This system contains neither harmful transition metals such as Cr(VI) nor co-catalysts such as phase-transfer catalysts. iii) This system has the advantage of using chlorine which is one of the most inexpensive oxidant.

Experimental

Materials. Extra pure grade cycloalkanols were obtained from Tokyo Kasei Co. and used without further purification. Solvents were distilled over common drying agents. 1-Oxo-4-methoxy-2,2,6,6-tetramethypiperidinium chloride (**2**) as well as nitroxide radical (**1**) were prepared by the previously reported method.[2b)]

GC Experiments. Typical procedure. To a solution containing cyclopentanol (100 mg, 1.16 mmol) and dodecane as an internal standard in dichloromethane (10 ml) was added freshly prepared **2** (299 mg, 1.0 equiv) at room temperature. Yield of the product was determined by GC using an internal standard.

Isolation Experiments. The oxidation was carried out using 2.0 mmol of an alcohol with 3.0 mmol of **2** in dichloromethane (10 ml) at room temperature for 30 min. The solvent was evaporated and subsequently diluted with a small amount of ether. Precipitated hydroxylamine hydrochloride **4** was filtered off and the solvent was evaporated. By the distillation of the residue under reduced pressure, the corresponding ketone, which had the identical IR spectrum with the authentic spectrum,[10)] was isolated.

Catalytic Oxidations. Into a mixture of cyclohexanol (200 mg, 2 mmol), **1** (37 mg, 0.2 mmol), finely ground Na_2CO_3 (1.5 g, 14 mmol), and chlorobenzene (internal standard) in dichloromethane (20 ml), gaseous chlorine was slowly bubbled through a Teflon tube using microfeeder (equipped with a 100 ml syringe). Every introduction of 5 ml of chlorine, the reaction progress was monitored by GC. The products other than cycloalkanone detected were identified by means of GC-mass spectroscopy. Monochlorocycloalkanones as well as higher chlorinated cycloalkanones were detected in some cases.

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